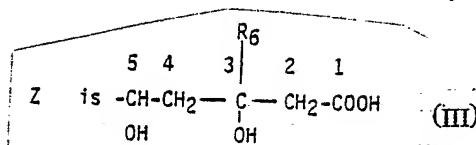
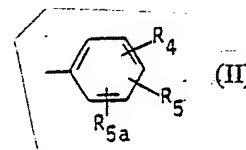
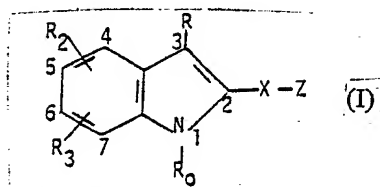




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification³ : C07D209/18, 405/04 A61K 31/405 | | A1 | (11) International Publication Number: WO 84/ 02131 (43) International Publication Date: 7 June 1984 (07.06.84) |
| (21) International Application Number: PCT/EP83/00308 (22) International Filing Date: 18 November 1983 (18.11.83) (31) Priority Application Numbers: 443,668 548,850 (32) Priority Dates: 22 November 1982 (22.11.82) 4 November 1983 (04.11.83) (33) Priority Country: US (71) Applicant: SANDOZ AG [CH/CH]; Lichtstrasse 35, CH-4002 Basel (CH). (72) Inventor: KATHAWALA, Faizulla, Gulamhusein ; 39 Woodland Avenue, Mountain Lakes, NJ 07946 (US). (81) Designated States: AU, DK, FI, HU, JP. | | | Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |

(54) Title: ANALOGS OF MEVALOLACTONE AND DERIVATIVES THEREOF, PROCESSES FOR THEIR PRODUCTION, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE AS PHARMACEUTICALS



(57) Abstract

Compounds of formula I wherein one of R and R₀ is II and the other is primary or secondary C₁₋₆alkyl, C₃₋₆cycloalkyl or phenyl-(CH₂)_m-, wherein R₄ is hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, R₅ is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, R_{5a} is hydrogen, C₁₋₂alkyl, C₁₋₂alkoxy, fluoro or chloro, and m is 1, 2 or 3, with the provisos that both R₅ and R_{5a} must be hydrogen when R₄ is hydrogen, R_{5a} must be hydrogen when R₅ is hydrogen, not more than one of R₄ and R₅ is trifluoromethyl, not more than one of R₄ and R₅ is phenoxy and not more than one of R₄ and R₅ is benzyloxy, R₂ is hydrogen, C₁₋₄alkyl, C₃₋₆cycloalkyl, C₁₋₄alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, R₃ is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R₃ must be hydrogen when R₂ is hydrogen, not more than one of R₂ and R₃ is trifluoromethyl, not more than one of R₂ and R₃ is phenoxy, and not more than one of R₂ and R₃ is benzyloxy, X is -(CH₂)_n- or -CH=CH- (n=0, 1, 2 or 3), Z is III wherein R₆ is hydrogen or C₁₋₃alkyl in free acid form or in the form of a physiologically-hydrolyzable and -acceptable ester or a lactone thereof or in salt form. These compounds are indicated for use as pharmaceuticals particularly for inhibiting cholesterol biosynthesis and treating atherosclerosis.

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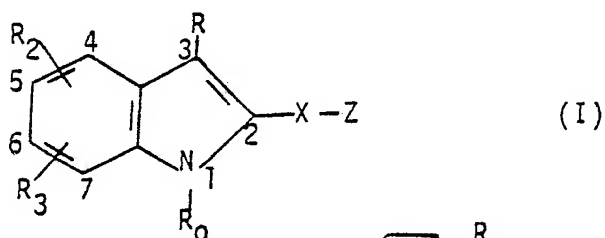
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ANALOGS OF MEVALOLACTONE AND DERIVATIVES THEREOF, PROCESSES FOR
THEIR PRODUCTION, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND
THEIR USE AS PHARMACEUTICALS

The invention concerns heterocyclic analogs of mevalono
lactone and derivatives thereof; processes for their production,
pharmaceutical compositions containing them and their use as
pharmaceuticals in particular as hypolipoproteinemic and anti-
5 atherosclerotic agents.

The invention is especially concerned with compounds of
formula I



wherein one of R and R₀ is and the other is

primary or secondary C₁₋₆alkyl, C₃₋₆cycloalkyl or
10 phenyl-(CH₂)_m-,

wherein R₄ is hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy,
(except t-butoxy), trifluoromethyl,
fluoro, chloro, phenoxy or benzyloxy,

R₅ is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy,
trifluoromethyl, fluoro, chloro,
15 phenoxy or benzyloxy,

R_{5a} is hydrogen, C₁₋₂alkyl, C₁₋₂alkoxy,
fluoro or chloro, and

m is 1, 2 or 3,

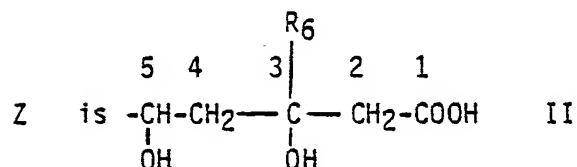
-2-

with the provisos that both R₅ and R_{5a} must be hydrogen when R₄ is hydrogen, R_{5a} must be hydrogen when R₅ is hydrogen, not more than one of R₄ and R₅ is trifluoromethyl, not more than one of R₄ and R₅ is phenoxy and not more than one of R₄ and R₅ is benzyloxy,

R₂ is hydrogen, C₁-4alkyl, C₃-6cycloalkyl, C₁-4alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R₃ is hydrogen, C₁-3alkyl, C₁-3alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R₃ must be hydrogen when R₂ is hydrogen, not more than one of R₂ and R₃ is trifluoromethyl, not more than one of R₂ and R₃ is phenoxy, and not more than one of R₂ and R₃ is benzyloxy,

X is -(CH₂)_n- or -CH=CH- (n=0, 1, 2 or 3),



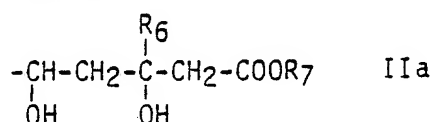
wherein R₆ is hydrogen or C₁-3alkyl in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a δ lactone thereof or in salt form.

By the term "physiologically-hydrolysable and -acceptable ester" is meant an ester of a compound in accordance with the invention in which the carboxyl moiety is esterified, and which



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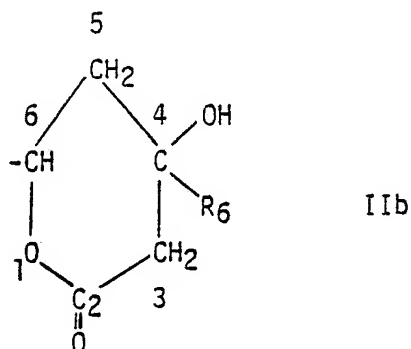
is hydrolysable under physiological conditions to yield an alcohol which is itself physiologically acceptable, e.g. non-toxic at desired dosage levels. Preferred such esters as Z can be represented together with the free acid by formula IIa



wherein R₇ is hydrogen, C₁-4alkyl or benzyl preferably hydrogen, C₁-3alkyl, n-butyl, i-butyl, t-butyl or benzyl and R₆ is as defined above.

When in salt form R₇ represents a cation.

When Z is in lactone form it forms a δ -lactone of formula IIb



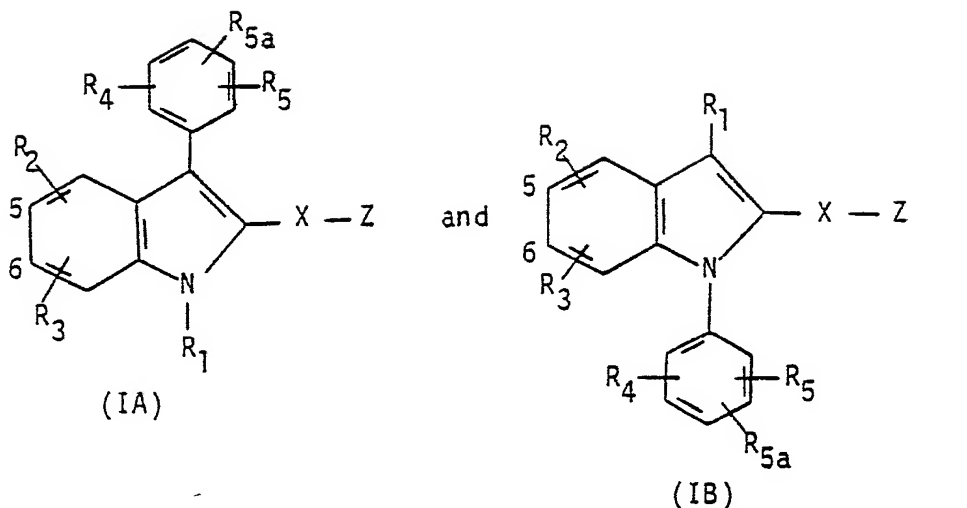
and references to "lactone" hereinafter refer to δ -lactones.

Salts of the compounds of the invention, e.g. of the compounds of formula I, include in particular their pharmaceutically acceptable salts. Such pharmaceutically acceptable salts include e.g. alkali metal salts such as the sodium and potassium salts and ammonium salts.

References to compounds of formula I, and sub-species thereof are intended to cover all forms unless otherwise stated.

The compounds of formula I may be divided into two groups, the compounds of formula IA and IB:

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wherein R_1 is primary or secondary C_{1-6} alkyl, C_{3-6} cycloalkyl or phenyl- $(CH_2)_m$ -, and
 R_2 - R_{5a} , X, Z and m are as defined above.

The compounds of formula IA may be divided into two sub-
 5 groups, the compounds wherein Z is a group of formula II in other than lactone form (Group IAa) and those wherein Z is a group of formula IIb (Group IAb). Likewise, the compounds of formula IB may be divided into two sub-groups, the compounds wherein Z is a group of formula II in other than lactone form (Group IBa) and
 10 those wherein Z is a group of formula IIb (Group IBb).

As is self-evident to those in the art, each compound of formula I (and every sub-scope and species thereof) has at least two centers of asymmetry (e.g. the two carbon atoms bearing the hydroxy groups in the group of formula IIa and the carbon
 15 atom bearing the hydroxy group and the carbon atom having the free valence in the group of formula IIb) and these lead to four stereoisomeric forms (enantiomers) of each compound (two racemates or pairs of diastereoisomers). These four stereoisomers may be designated as the R,R; R,S; S,R; and S,S enantiomers, all four
 20 stereoisomers being within the scope of this invention. Depending

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on the nature of substituents further assymetric carbon atoms may be present and the resulting isomers and mixtures thereof also form part of the invention. Compounds containing only two centres of assymetry (four mentioned stereoisomers) are preferred.

5 R_1 is preferably primary or secondary C_{1-6} alkyl not containing assymetric carbon atom (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, 1-ethylpropyl, neopentyl and n-hexyl), more preferably C_{1-3} alkyl and most preferably methyl, ethyl or i-propyl, especially i-propyl.

10 Alkyl as R_2 is preferably C_{1-3} or n-, i- or t-butyl and alkoxy C_{1-3} or n- or i-butoxy. R_2 is preferably R_2' , where R_2' is hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, more preferably R_2'' , where R_2'' is hydrogen, C_{1-3} alkyl, methoxy, fluoro, chloro or 4-, 5- or 6-benzyloxy, and
15 most preferably R_2''' , where R_2''' is hydrogen, C_{1-3} alkyl or 4- or 6-benzyloxy, especially hydrogen or methyl and most especially hydrogen.

20 R_3 is preferably R_3' , where R_3' is hydrogen, C_{1-3} alkyl, C_{1-2} alkoxy, fluoro or chloro, more preferably R_3'' , where R_3'' is hydrogen or C_{1-3} alkyl and most preferably R_3''' , where R_3''' is hydrogen or methyl, especially hydrogen. R_3 (R_3' , etc.) must be hydrogen when R_2 (R_2' , etc.) is hydrogen.

25 Preferably, when R_2 (R_2' , R_2'' , etc.) is other than hydrogen and R_3 (R_3' , R_3'' , etc.) is hydrogen, R_2 (R_2' , etc.) is in the 4-, 5- or 6-position.

30 Preferably, when both R_2 (R_2' , R_2'' , etc.) and R_3 (R_3' , R_3'' , etc.) are other than hydrogen, at least one of them is in the 5- or 6-position, neither of them is in the 7-position, and not more than one of them is a member of the group consisting of t-butyl, C_3-6 cycloalkyl, trifluoromethyl, phenoxy and benzyloxy; more preferably, they are not ortho to each other when neither of them is a member of the group consisting of methyl, methoxy, fluoro and chloro. Most preferably, one is in the 4-position and the other is in the 6-position.

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Except where otherwise indicated: (a) Any C₁₋₄alkyl or C₃₋₆cycloalkyl group as R₂, R_{2'}, R₃, R_{3'}, etc. is more preferably in the 4- or 6-position. (b) Any C₁₋₄alkoxy, fluoro or chloro substituent as R₂, R_{2'}, R₃, R_{3'}, etc. is more preferably in the 5-position. (c) Any benzyloxy as R₂, R_{2'}, R₃, R_{3'}, etc. is more preferably in the 4-, 5- or 6-position and most preferably in the 4- or 6-position, especially the 6-position.

Alkyl as R₄ is preferably C₁₋₃ or n-, i- or t-butyl and alkoxy C₁₋₃ or n- or i-butoxy. R₄ is preferably R_{4'}, where R_{4'} is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, more preferably R_{4''}, where R_{4''} is hydrogen, methyl, methoxy, fluoro or chloro, and most preferably R_{4'''}, where R_{4'''} is hydrogen, methyl or fluoro, especially R_{4'''}, where R_{4'''} is hydrogen, 3- or 4-methyl or 4-fluoro and most especially 4-fluoro.

R₅ is preferably R_{5'}, where R_{5'} is hydrogen, C₁₋₂alkyl, C₁₋₂alkoxy, fluoro or chloro, more preferably R_{5''}, where R_{5''} is hydrogen, methyl, methoxy, fluoro or chloro, and most preferably R_{5'''}, where R_{5'''} is hydrogen or methyl, especially hydrogen. R₅ (R_{5'}, R_{5''}, etc.) must be hydrogen when R₄ (R_{4'}, R_{4''}, etc.) is hydrogen.

R_{5a} is preferably R_{5a'}, where R_{5a'} is hydrogen or methyl, and most preferably hydrogen. R_{5a} (R_{5a'}, etc.) must be hydrogen when at least one of R₄ (R_{4'}, R_{4''}, etc.) and R₅ (R_{5'}, R_{5''}, etc.) is hydrogen.

Preferably, when R₄ (R_{4'}, R_{4''}, etc.) is other than hydrogen and R₅ (R_{5'}, R_{5''}, etc.) and R_{5a} (R_{5a'}, etc.) are both hydrogen, R₄ (R_{4'}, etc.) is in a meta or para position, more preferably the para position. The most preferred monosubstituted phenyl group is 4-fluorophenyl.



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Preferably, when both R_4 (R_4' , R_4'' , etc.) and R_5 (R_5' , R_5'' , etc.) are other than hydrogen and R_{5a} (R_{5a}' , etc.) is hydrogen, at least one of R_4 (R_4' , etc.) and R_5 (R_5' , etc.) is in a meta or para position (more preferably both are), and not more than one of them is a member of the group consisting of t-butyl, trifluoromethyl, phenoxy and benzyloxy; more preferably, R_4 (R_4' , etc.) and R_5 (R_5' , etc.) are not ortho to each other when neither of them is a member of the group consisting of methyl, methoxy, fluoro and chloro. The most preferred disubstituted phenyl groups are 3,4- and 3,5-dimethylphenyl and 4-fluoro-3-methylphenyl, especially 3,5-dimethylphenyl and 4-fluoro-3-methylphenyl.

Preferably, when each of R_4 (R_4' , etc.), R_5 (R_5' , etc.) and R_{5a} (R_{5a}' , etc.) is other than hydrogen, at least two of them (more preferably, all three) are in meta or para positions, and not more than one of them is a member of the group consisting of t-butyl, trifluoromethyl, phenoxy and benzyloxy; more preferably, no two of them are ortho to each other unless at least one member of the each pair of substituents that are ortho to each other is a member of the group consisting of methyl, methoxy, fluoro and chloro. The most preferred trisubstituted phenyl group is 3,5-dimethyl-4-fluorophenyl.

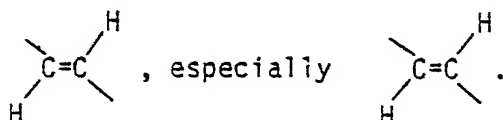
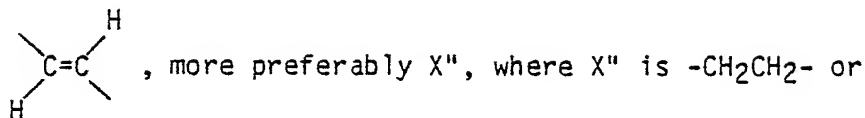
R_6 is preferably R_6' , where R_6' is hydrogen or C_{1-2} alkyl, more preferably R_6'' , where R_6'' is hydrogen or methyl, and most preferably hydrogen.

R_7 is preferably R_7' , where R_7' is hydrogen or C_{1-3} alkyl more preferably R_7'' , where R_7'' is hydrogen or C_{1-2} alkyl. Such compounds wherein Z is of formula II or IIa are most preferably in salt form. Preferred salt-forming cations are those free from centres of assymetry especially e.g. sodium, potassium or ammonium most preferably sodium.



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X is preferably X', where X' is $-(CH_2)_m-$ or



Z is preferably a group of formula IIa wherein R_6 is R_6' and
 5 R_7 is R_7' or a group of formula IIb wherein R_6 is R_6' , more preferably a group of formula IIa wherein R_6 is R_6'' and R_7 is R_7'' or a group of formula IIb wherein R_6 is R_6'' and most preferably a group of formula IIa wherein R_6 is hydrogen and R_7 is R_7'' or a group of formula IIb wherein R_6 is hydrogen, especially a group
 10 of formula IIa wherein R_6 is hydrogen in salt form particularly in sodium salt form or a group of formula IIb wherein R_6 is hydrogen.

n is preferably m, where m is 1, 2 or 3, preferably 2 or 3 and most preferably 2.

15 Insofar as the compounds of Groups IAa and IBa are concerned, the erythro isomers are generally preferred over the threo isomers, erythro and threo referring to the relative positions of the hydroxy groups in the 3- and 5-positions (of the group of formula II and IIa).

20 As between compounds of formula I having identical R, R_0 , R_2 , R_3 , R_6 and X groups, free acid, salt and ester forms are generally preferred to lactone forms.

The preferred stereoisomers of the compounds having only two assymetric carbons wherein X is a direct bond or $-CH=CH-$, and
 25 Z is in other than lactone form are the 3R,5S and 3R,5R isomers and the racemate of which each is a constituent, i.e., the 3R,5S-3S,5R (erythro) and 3R,5R-3S,5S (threo) racemates, with the 3R,5S isomer and the racemate of which it is a constituent being more preferred and the 3R,5S isomer being most preferred.



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The preferred stereoisomers of the compounds having only two assymetric carbons wherein X is $-(CH_2)_m-$, and Z is in other than lactone form are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, i.e., the 3R,5R-3S,5S (erythro) and 3R,5S-3S,5R (threo) racemates, with the 3R,5R isomer and the racemate of which it is a constituent being more preferred and the 3R,5R isomer being most preferred.

The preferred stereoisomers of the compounds having only two assymetric carbons wherein X is a direct bond or $CH=CH-$, and Z is a group of formula I Ib are the 4R,6S and 4R,6R isomers and the racemate of which each is a constituent, i.e., the 4R,6S-4S,6R (trans lactone) and 4R,6R-4S,6S (cis lactone) racemates, with the 4R,6S isomer and the racemate of which it is a constituent being more preferred and the 4R,6S isomer being most preferred.

The preferred stereoisomers of the compounds having only two assymetric carbons wherein X is $-(CH_2)_m-$, and Z is a group of formula I Ib are the 4R,6R and 4R,6S isomers and the racemate of which each is a constituent, i.e., the 4R,6R-4S,6S (trans lactone) and 4R,6S-4S,6R (cis lactone) racemates, with the 4R,6R isomer and the racemate of which it is a constituent being more preferred and the 4R,6R isomer being most preferred.

Each of the preferences set forth above applies, not only to the compounds of formula I but also to the compounds of formulae IA and IB and those of Groups IAa, IAb, IBa and IBb as well as to every other subgroup thereof set forth infra, e.g., Groups (i)-(cxiv), unless otherwise indicated. When any preference contains a variable, the preferred significances of that variable apply to the preference in question, unless otherwise indicated.



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Preferred groups of compounds of formula I include the compounds

(i) of Group IAa wherein R_1 is R_1' , R_2 is R_2' , R_3 is R_3' , R_4 is R_4' , R_5 is R_5' , R_{5a} is R_{5a}' , R_6 is R_6' , R_7 is R_7' , and X is X' ,

(ii) of (i) wherein when R_2' is other than hydrogen and R_3' is hydrogen, R_2' is in the 4-, 5- or 6-position; when both R_2' and R_3' are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the 7-position; when both R_4' and R_5' are other than hydrogen and R_{5a}' is hydrogen, at least one of R_4' and R_5' is in a meta or para position; and when each of R_4' , R_5' and R_{5a}' is other than hydrogen, at least two of them are in meta or para positions,

(iii)-(iv) of (i) and (ii) wherein R_6 is R_6'' , especially hydrogen,

(v)-(vi) of (i) and (ii) wherein R_1 is C_{1-3} alkyl, R_2 is R_2'' , R_3 is R_3'' , R_4 is R_4'' , R_5 is R_5'' , R_6 is R_6'' , especially hydrogen, R_7 is R_7'' , and X is X'' ,

(vii) of (i) wherein R_1 is C_{1-3} alkyl, R_2 is R_2''' , R_3 is R_3''' , R_4 is R_4''' , R_5 is R_5''' , R_{5a} is hydrogen, R_6 is

hydrogen, R_7 is R_7'' , and X is

$$\begin{array}{c} \text{H} \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{H} \end{array},$$

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(viii)-(xiii) of (i)-(vi) wherein any salt is a sodium potassium or ammonium salt.

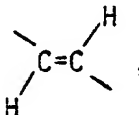
(xiv) of Group IAb wherein R_1 is R_1' , R_2 is R_2' , R_3 is R_3' , R_4 is R_4' , R_5 is R_5' , R_{5a} is R_{5a}' , R_6 is R_6' and X is X' ,

5 (xv) of (xiv) wherein when R_2' is other than hydrogen and R_3' is hydrogen, R_2' is in the 4-, 5- or 6-position; when both R_2' and R_3' are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the 7-position; when both R_4' and R_5' are other than hydrogen and R_{5a}' is
10 hydrogen, at least one of R_4' and R_5' is in meta or para position; and when each of R_4' , R_5' and R_{5a}' is other than hydrogen, at least two of them are in meta or para positions,

(xvi)-(xvii) of (xiv) and (xv) wherein R_6 is R_6'' , especially hydrogen,

15 (xviii)-(xix) of (xiv) and (xv) wherein R_1 is C_{1-3} alkyl, R_2 is R_2'' , R_3 is R_3'' , R_4 is R_4'' , R_5 is R_5'' , R_6 is R_6'' especially hydrogen, and X is X'' ,

(xx) of (xiv) wherein R_1 is C_{1-3} alkyl, R_2 is R_2''' , R_3 is R_3''' , R_4 is R_4''' , R_5 is R_5''' , R_{5a} is hydrogen, R_6 is hydrogen,

20 and X is ,

(xxi) of Group IBa wherein R_1 is R_1' , R_2 is R_2' , R_3 is R_3' , R_4 is R_4' , R_5 is R_5' , R_{5a} is R_{5a}' , R_6 is R_6' , R_7 is R_7' , and X is X' ,

25 (xxii) of (xxi) wherein when R_2' is other than hydrogen and R_3' is hydrogen, R_2' is in the 4-, 5- or 6-position; when both R_2' and R_3' are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the 7-position; when both R_4' and R_5' are other than hydrogen and R_{5a}' is
30 hydrogen, at least one of R_4' and R_5' is in a meta or para position; and when each of R_4' , R_5' and R_{5a}' is other than hydrogen, at least two of them are in meta or para positions,

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(xxiii)-(xxiv) of (xxi) and (xxii) wherein R_6 is R_6'' , especially hydrogen,

(xxv)-(xxvi) of (xxi) and (xxii) wherein R_1 is C_{1-3} alkyl, R_2 is R_2'' , R_3 is R_3'' , R_4 is R_4'' , R_5 is R_5'' , R_6 is R_6'' , especially hydrogen, R_7 is R_7'' , and X is X'' ,

(xxvii)-(xxxii) of (xxi)-(xxvi) wherein any salt is a sodium potassium or ammonium salt.

(xxxiii) of Group IBb wherein R_1 is R_1' , R_2 is R_2' , R_3 is R_3' , R_4 is R_4' , R_5 is R_5' , R_{5a} is R_{5a}' , R_6 is R_6' and X is X' ,

(xxxiv) of (xxxiii) wherein when R_2' is other than hydrogen and R_3' is hydrogen, R_2' is in the 4-, 5- or 6-position; when both R_2' and R_3' are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the 7-position; when both R_4' and R_5' are other than hydrogen and R_{5a}' is hydrogen, at least one of R_4' and R_5' is in a meta or para position; and when each of R_4' , R_5' and R_{5a}' is other than hydrogen, at least two of them are in meta or para positions,

(xxxv)-(xxxvi) of (xxxiii) and (xxxiv) wherein R_6 is R_6'' , especially hydrogen,

(xxxvii)-(xxxviii) of (xxxiii) and (xxxiv) wherein R_1 is C_{1-3} alkyl, R_2 is R_2'' , R_3 is R_3'' , R_4 is R_4'' , R_5 is R_5'' , R_6 is R_6'' , especially hydrogen, and X is X'' ,

(xxxix)-(lxiii) of (i)-(xiii) and (xxi)-(xxxii) wherein the hydroxy groups in the 3- and 5-positions (of the group of formula IIa) have the erythro configuration,

(lxiv)-(lxxxviii) the 3R,5S enantiomers of the compounds of

(xxxix)-(lxiii) wherein X is $\begin{array}{c} \diagup \\ \text{C}=\text{C} \\ \diagdown \end{array} \begin{array}{c} \text{H} \\ \\ \text{H} \end{array}$ and the 3R,5R enantiomers

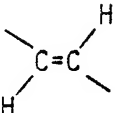
of the compounds of these groups wherein X is $-(CH_2)_m-$,

(lxxxix)-(ci) of (xiv)-(xx) and (xxxiii)-(xxxviii) wherein the hydroxy group on the lactone ring IIb is trans to X (i.e., the trans lactones), and



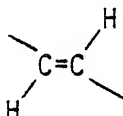
-13-

(cii)-(cxiv) the 4R,6S enantiomers of the compounds of

(lxxxix)-(ci) wherein X is  and the 4R,6R

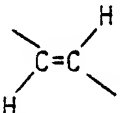
enantiomers of the compounds of these groups wherein X is $-(CH_2)_m-$.

5 Groups (xxxiv)-(lxiii) embrace the 3R,5S-3S,5R racemate and the 3R,5S and 3S,5R enantiomers of the compounds wherein X is

 (the 3S,5R enantiomer being least preferred)

and the 3R,5R-3S, 5S racemate and the 3R,5R and 3S,5S enantiomers of the compounds wherein X is $-(CH_2)_m-$ (the 3S,5S enantiomer
10 being least preferred).

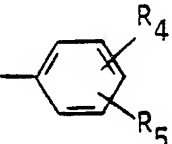
Groups (lxxxix)-(ci) embrace the 4R,6S-4S,6R racemate and the 4R,6S and 4S,6R enantiomers of the compounds wherein X is

 (the 4S,6R enantiomer being least preferred) and

the 4R,6R-4S,6S racemate and the 4R,6R and 4S,6S enantiomers of the compounds wherein X is $-(CH_2)_m-$, (the 4S,6S enantiomer being
15 least preferred).

In the above mentioned compound groups (i) to (cxiv) those containing a carboxyl group are preferably in salt form with a cation free from asymmetric carbon atoms e.g. sodium, potassium
20 or ammonium especially sodium.

A particular compound group covers those of formula I

wherein one of R and R₀ is  and the other is

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C₁₋₃alkyl, n-butyl or i-butyl,wherein R₄ is hydrogen, C₁₋₃alkyl, n-butyl,i-butyl, C₁₋₃alkoxy, n-butoxy,

i-butoxy, trifluoromethyl, fluoro,

chloro, phenoxy or benzyloxy, and

R₅ is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy,

trifluoromethyl, fluoro, chloro,

phenoxy, or benzyloxy,

with the provisos that not more

than one of R₄ and R₅ is trifluoro-methyl, not more than one of R₄ andR₅ is phenoxy, and not more thanone of R₄ and R₅ is benzyloxy,R₂ is hydrogen, C₁₋₃alkyl, n-butyl, i-butyl,C₁₋₃alkoxy, n-butoxy, i-butoxy, trifluoro-

methyl, fluoro, chloro, phenoxy or benzyloxy,

R₃ is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoro-

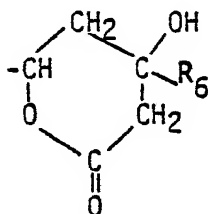
methyl, fluoro, chloro, phenoxy or benzyloxy,

with the provisos that not more than one of R₂and R₃ is trifluoromethyl, not more than oneof R₂ and R₃ is phenoxy, and not more than oneof R₂ and R₃ is benzyloxy,

X is $-(CH_2)_n-$ or $\begin{array}{c} \text{H} \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{H} \end{array}$,

wherein n is 0, 1, 2 or 3, and

Z is $\begin{array}{c} \text{R}_6 \\ | \\ -\text{CH}-\text{CH}_2-\text{C}-\text{CH}_2-\text{COOR}_7' \\ | \quad \quad | \\ \text{OH} \quad \quad \text{OH} \end{array}$ or

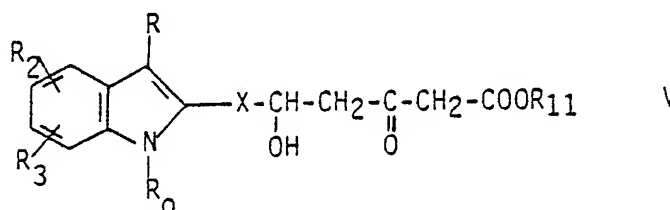


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wherein R_6 is hydrogen or C_{1-3} alkyl, and
 R_7' is hydrogen, C_{1-3} alkyl, n-butyl,
 i-butyl, t-butyl, benzyl or M,
 wherein M is a pharmaceutically
 acceptable cation.

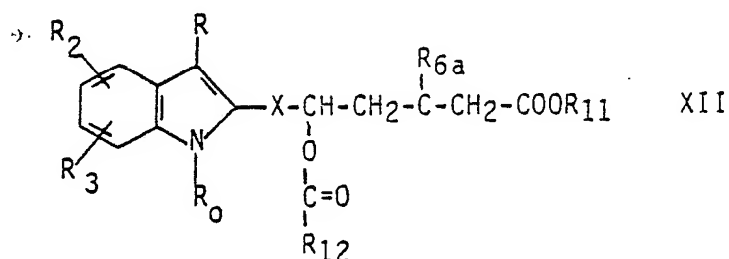
The compounds of formula I can be prepared by

a) when R_6 is hydrogen, reducing a compound of formula V



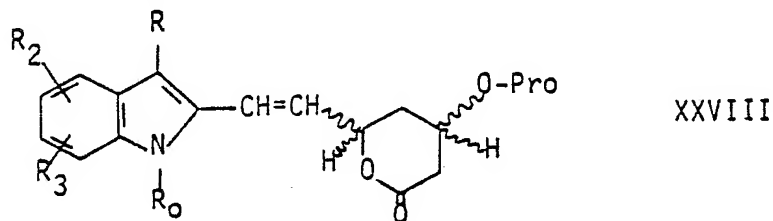
wherein R_{11} is a radical forming a physiologically-
 hydrolysable and -acceptable ester and X, R, R_0 , R_2 and R_3
 are as defined above,

b) when $R_6 = C_{1-3}$ alkyl, hydrolysing a compound of
 formula XII



wherein R_{6a} is C_{1-3} alkyl, R_{12} is an ester forming group
 and X, R, R_0 , R_3 and R_{11} are as defined above,

c) when X is $-CH=CH-$ deprotecting a compound of formula XXVIII



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wherein Pro is a protecting group and R, R₀, R₂ and R₃ are as defined above,

d) hydrolysing a compound of formula I in the form of a physiologically-hydrolysable ester or a lactone or

5 e) esterifying or lactonising a compound of formula I in free acid form,

and when a free carboxyl group is present, recovering the compound obtained in free acid form or in the form of a salt. In processes a) and b) R₁₁ is preferably C₁₋₂alkyl especially methyl and R₁₂ is preferably C₁₋₃alkyl, especially C₁₋₂alkyl, in particular methyl.

It will readily be appreciated that the various forms of the compounds of formula I may interconverted as indicated in d) and e) above.

In the same way compounds obtained according to a), b), and c) may be hydrolysed to free acid forms and free acid forms may be esterified or lactonised to produce a desired end-product. The invention thus also provides a process for preparing a compound of formula I which comprises hydrolysing a compound of formula I in ester or lactone form or esterifying or lactonising a compound of formula I in free acid form and when a free carboxyl group is present recovering the compound obtained in free acid form or in the form of a salt.

25 Unless otherwise stated reactions are performed in a manner conventional for the type of reaction involved. Molar ratios and reaction times are as a rule conventional and non-critical and are chosen according to principles well established in the art on the basis of reactants and conditions employed.

30 Solvents, alone or as mixtures, are generally chosen which remain inert and liquid during the reaction in question.

Examples of inert atmospheres are carbon dioxide and more usually nitrogen or a noble gas, nitrogen being preferred. Most reactions, including those wherein use of an inert atmosphere is not mentioned, are carried out in such for convenience.



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Reduction according to a) is preferably carried out using a mild reducing agent such as sodium borohydride or, preferably, a complex of t-butylamine and borane in an inert organic solvent such as a lower alkanol, preferably ethanol, conveniently at a temperature of -10° to 30°C, under an inert atmosphere.

Use of an optically pure starting material will lead to only two optical isomers (diastereoisomers) of the resulting end product. However, if stereospecificity is desired it is preferred to utilize a stereoselective reduction in order to maximize production of a mixture of the erythro stereoisomers (racemate) of which the preferred stereoisomer (as set forth above) is a constituent. Stereoselective reduction is preferably carried out in three steps. For example in the first step, the ketoester of formula V is treated with a tri(primary or secondary C₂₋₄alkyl)borane, preferably triethylborane or tri-n-butylborane, and air to form a complex. The reaction temperature is suitably 0° to 50°C, preferably 20° to 30°C. The first step is carried out in an anhydrous inert organic solvent, preferably an ether solvent such as tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane or 1,2-diethoxyethane, with tetrahydrofuran, being the most preferred solvent. In the second step, for example, the complex is reduced with sodium borohydride, preferably in the same solvent as utilized for the first step, at -100° to -40°C, preferably -90° to -70°C. In the third step, the product of the second step is, for example, treated with, preferably, anhydrous methanol at 20° to 40°C, preferably 20° to 30°C. The amount of methanol is not critical. However, a large excess, e.g., 50-500 moles per mole of ketoester of formula V, is typically utilized.

Hydrolysis according to b) or d) is carried out in a manner conventional for such reactions e.g. employing an inorganic



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hydroxide such as NaOH or KOH with, if desired subsequent acidification to give the free acid form. Suitable solvents are mixtures of water and water miscible solvents such as lower alkanols e.g. methanol or ethanol and reaction conveniently takes
5 place at temperatures from 20°C to reflux preferably not more than 80°C. If it is desired to recover the compound in a salt form corresponding to the cation of the hydroxide employed then slightly less than equivalent amounts of the latter may be employed. In b) R₁₂ will conveniently be the same as R₁₁ e.g.
10 C₁₋₃alkyl, especially C₁₋₂alkyl, preferably methyl.

Lactonisation according to e) is carried out in conventional manner e.g. by heating the corresponding acid in an anhydrous inert organic solvent e.g. a hydrocarbon such as benzene, toluene or a xylene or mixtures thereof, preferably at
15 temperatures of 75°C to reflux although more preferably not above 150°C. Preferably, however, a lactonisation agent, e.g. a carbodiimide, preferably a water-soluble carbodiimide such as N-cyclohexyl-N'-[2-(N"-methylmorpholinium)ethyl]carbodiimide p-toluenesulfonate, in an anhydrous inert organic solvent, e.g., a
20 halogenated lower alkane, preferably methylene chloride is employed. Reaction temperatures then lie typically between 10° and 35°C, especially 20° to 30°C.

As is evident to those in the art, a racemic threo 3,5-dihydroxycarboxylic acid yields a racemic cis lactone and a racemic
25 erythro 3,5-dihydroxycarboxylic acid yields a racemic trans lactone. Use of a mixture of threo and erythro 3,5-dicarboxylic acid yields a mixture of cis and trans lactones (all four possible diastereoisomers). Likewise if a single enantiomer of the 3,5-dihydroxycarboxylic acid is utilized, a single enantiomer
30 of the lactone is obtained. For example, lactonisation of a 3R,5S erythro dihydroxycarboxylic acid yields a 4R,6S lactone.

Esterification according to e) is conventional employing e.g. a large excess of a compound R₁₁OH wherein R₁₁ is as defined above at 20°C to 40°C in the presence of a catalytic amount of an



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acid such as p-toluenesulfonic acid. Where methyl esters are required these can also be obtained e.g. using diazomethane in an anhydrous inert ether solvent such as tetrahydrofuran, 1,2-dimethoxyethane or 1,2-diethoxyethane and especially diethyl-
5 ether at e.g. 0° to 30°C preferably 20° to 30°C.

Examples of protecting groups in reaction c) are diphenyl-t-butylsilyl, tri-isopropylsilyl or dimethyl-t-butylsilyl, C₁₋₆n-alkyl, benzyl, triphenylmethyl, tetrahydrofuran-2-yl, tetrahydropyran-2-yl, 4-methoxytetrahydropyran-4-yl, C₁₋₆n-alkanoyloxy. Especially preferred are trisubstituted silyl radicals in particular diphenyl-t-butylsilyl.

Deprotection is carried out in conventional manner e.g. by cleavage under mild conditions such as employing e.g. for removal of a silyl containing group such as diphenyl-t-butylsilyl a fluoride reagent e.g. tetra-n-butyl-ammonium fluoride in an anhydrous inert organic medium preferably tetrahydrofuran containing glacial acetic acid at temperatures of 20° to 60°C especially 20° to 30°C. Preferably 1-4 moles of fluoride are used per mole of silyl group with 1.2 to 1.8 moles of glacial acetic acid to each mole of fluoride.

The required starting materials may be prepared for example as illustrated in the following reaction schemes. The symbols used are defined as follows

as R, R₀, R₁, R₂, R₃, R₄, R₅, R_{5a}, R₆, R_{6a}, R₁₁, R₁₂, X = as defined above.

R_{12a} = C₁₋₃alkyl, preferably C₁₋₂alkyl

Y = halogen, especially chloro or bromo, preferably chloro

Ac = acetyl

⓪ = phenyl

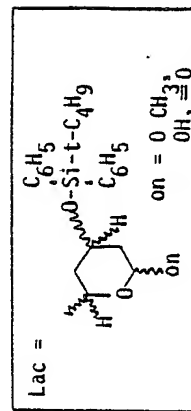
30 $\text{+} = \text{t-butyl}$

$$1ac = \text{Cyclohexane ring with } OH \text{ and } O-Si(C_6H_5)(C_4H_9) \text{ substituents}$$

[on=OCH₃(XXVI), OH(XXVII) or =O(XXVIII)]

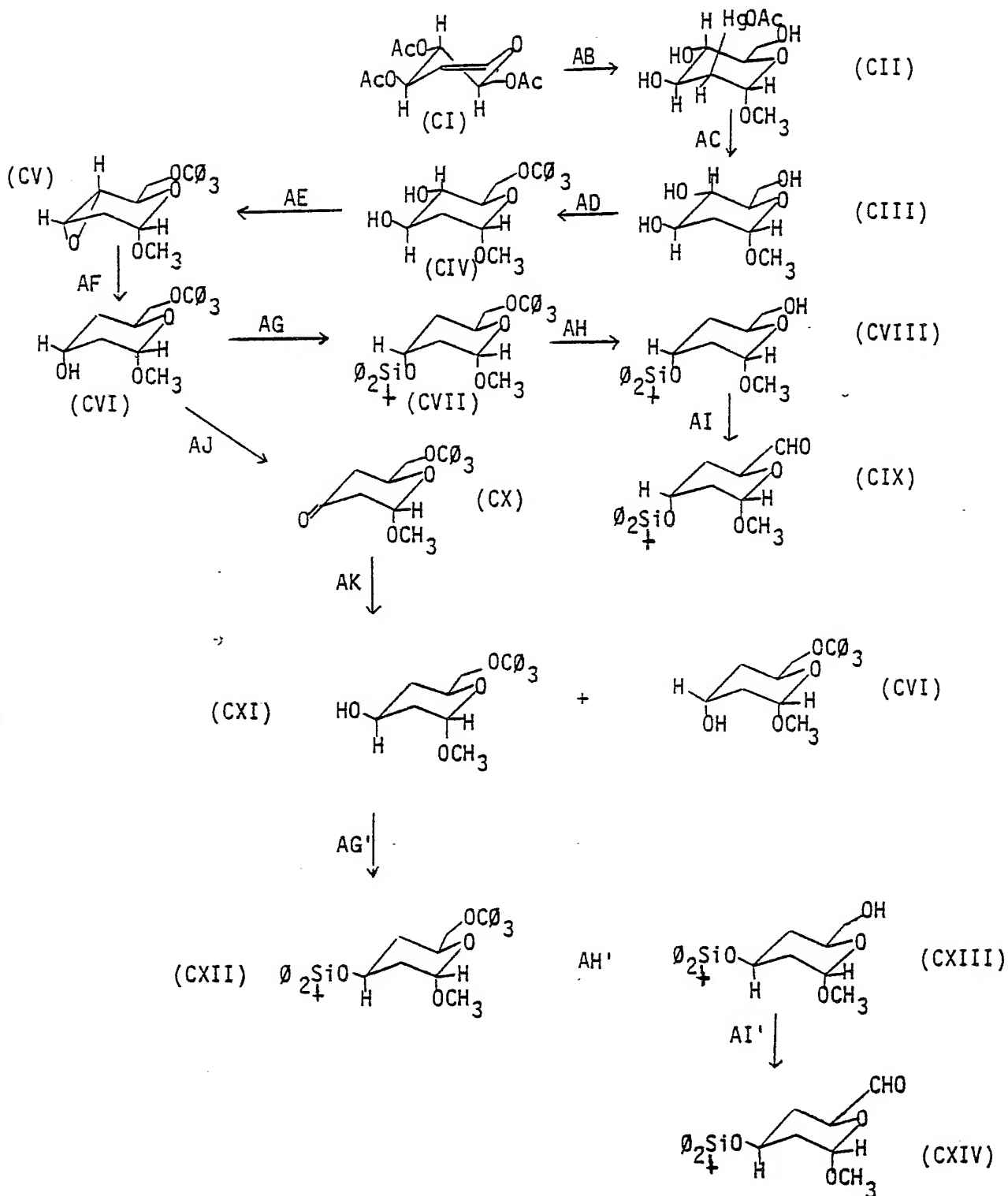


REACTION SCHEME II



Reaction Scheme III

Two isomers of the compound of formula XXV may be synthesized by the following series of reactions:



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Unless otherwise stated reactions are performed in a manner conventional for the type of reaction involved. Mol ratios and reaction times are as a rule conventional and non-critical and are chosen according to principles well established in the art on the basis of reactants and conditions employed.

Solvents, alone or as mixtures, are generally chosen which remain inert and liquid during the reaction in question.

Examples of inert atmospheres are carbondioxide and more usually nitrogen, helium, neon, argon or krypton, nitrogen being preferred. Most reactions, including those wherein use of an inert atmosphere is not mentioned are carried out in such for convenience.

The following tables give examples of typical reaction conditions in reaction schemes I and II temperatures are in degrees centigrade.

Abbreviations

THF (tetrahydrofuran)

DMF (dimethylformamide)



| Reaction | Type/Steps | Special conditions/ Reagents | Temperatures | Atmosphere | Solvents |
|------------------|--|---|---|--------------|--|
| (A) | 1. IVA + base 2. add IV | 1. Strong base e.g. n-butyl lithium for dianion, lithium diisopropylamide and NaH (latter for generation of monoanion only). pref. NaH for monoanion then nBuLi | -80° to 10° esp. -20° to 5° | inert gas | anhydrous THF, diethylether, 1,2-dimethoxy-, 1,2-diethoxy-ethane |
| (E) | 1. IVB + base 2. add IV | 1. Strong base as (A) preferred lithium diisopropylamide, Mol ratio of IVB to IV esp. 3:1 | -80° to -40° esp. -80° to -75° | inert gas | as (A) |
| (G) | acylation | base e.g. pyridine, tertiary amine such as trimethylamine, 4-dimethylaminopyridine | 10° to 50° esp. 20° to 30° | inert gas | excess pyridine and/or ether e.g. THF |
| (H) (cf. (F)) | 1. XIA + base 2. add XI | reagents as (A) Mol ratio of XIA to XI esp. 3:1 | 1. -80° to 0° 2. -80° to -40° esp. -80° to -70° | inert gas | as (A) esp. THF |
| (M) | reduction | metal hydride e.g. lithiumaluminium hydride diisobutylaluminium hydride | -80° to reflux pref. < 70° esp. -80° to 25° | | as (A) esp. THF |
| (N) | mild oxidation | e.g. MnO ₂ in large molar excess | 20° to reflux pref. < 80° | | as (A) |
| (O) | 1. cis-1-lithium-2-ethoxyethylene* 2. p.TsOH * prepared e.g. as described in the examples. | 1. 2. p-toluenesulfonic acid in catalytic amounts | 1. -80° to -40° esp. -80° to -70° | 1. inert gas | 1. anhydr. THF 2. THF + water |

| Reaction | Type/Steps | Special conditions/ Reagents | Temperatures | Atmosphere | Solvents |
|----------|---|---|---|----------------------|--|
| Ⓐ | Wittig | those usual for Wittig reactions | -20° to reflux pref. < 140° | inert gas | as Ⓐ or anhyd. hydrocarbon e.g. benzene, toluene |
| Ⓚ | 1. XXI + base 2. R ₁ -I | 1. base e.g. as Ⓐ esp. NaH | 1. -20° to 30° 2. -15° to reflux pref. < 80° esp. 20-30° | inert gas | as Ⓐ or anhyd. diethylacetamide and esp. dimethyl acetamide |
| ** Ⓡ | Vilsmeier-Haack 1. XIIIB + XIIIC 2. XIIIA + iminium salt from 1 3. add base | 1. Phosphorous oxychloride is pref. as XIIIB 3. aqueous NaOH, KOH | 1. 0° to 35° esp. 0° to 15° 2. 60° to 120° esp. 80° to 105° 3. 10° to 45° esp. 10°-25° | 1. inert gas 2. " | 1. and 2. anhydr. excess XIIIC alone or with lower alkylnitrile e.g. acetonitrile |
| Ⓢ | reduction | as Ⓜ pref. NaBH ₄ | -5° to 35° | inert gas | as Ⓐ or pref. when using NaBH ₄ ether + lower alkanol e.g. THF + methanol |
| Ⓣ | halogenation | phosphorous trihalide, thionylhalide or oxalyl halide (halide = Y) + optionally a trace of DMF | 20° to 35° for phosphorous tri- halide, otherwise -10° to 20° esp. -10° to 5° | inert gas | diethylether or THF |
| Ⓤ | halogenation | triphenylphosphine + CY ₄ | -10° to reflux pref. < 150° when run in excess CY ₄ 25° to reflux pref. < 100° | | excess CY ₄ or as Ⓟ |

** Mol ratio 1. 1-5 of XIIIB + 1 of XIIIC : 1 of XIIIA
3. >4 pref. 4 to 6 of base per 1 of XIIIB in first step

| Reaction | Type/Steps | Special conditions/ Reagents | Temperatures | Atmosphere | Solvents |
|----------|--|--|---|------------|--|
| ① | | triphenylphosphine | 60° to reflux pref. < 150° esp. 100°-110° | inert gas | anhydr. hydro- carbon e.g. benzene, toluene or a xylene |
| ② | Mittig Reaction 1. base 2. XXV | 1. as ① 2. produces mixture of cis(Z) and trans(E) which can be separated here (conventionally) or further reacted and separated at a later stage | 1. 0° to 25° 2. -10° to reflux pref. < 80° esp. 20° to 30° | inert gas | 1. + 2. as ① |
| ③ | hydrolysis | acid e.g. 10% HCl in THF or glacial CH ₃ COOH in THF/H ₂ O Reaction produces some "6"-epimerisation which is greater if HCl is used (pref. is glacial CH ₃ COOH/ THF/H ₂ O: 3/2/1) | 10° to 100° esp. 60° | | THF with water |
| ④ | oxidation (cf. Tetrahedron Letters 1976. pp. 2503-6) | a) mild conditions e.g. N-methylmorpholine oxide + dichlorotris((C ₆ H ₅) ₃ P)- ruthenium II or e.g. b) AgCO ₃ on celite | a) 0° to 40° pref. 20° to 30° b) 0° to reflux pref. < 150° esp. 100° to reflux | inert gas | a) anhydrous DMF, acetone b) as ⑤ |
| ⑤ | cf. ② 1. XXIIB + XXIID 2. XXIIA + iminium salt from 1. 3. add base | cf. ② | 1. -10° to 25° esp. -10° to 5° 2. 60° to 100° esp. 65° to 85° 3. 20° to 45° esp. 20° to 30° | inert gas | as ② |

| Reaction | Type/Steps | Special conditions/ Reagents | Temperatures | Atmosphere | Solvents |
|----------------|------------|--|--------------|------------|----------|
| BB CC DD | Wittig | <p>Successive Wittig reactions as (P) employing e.g.</p> <p>$(C_6H_5)_3P^{\theta}-CH_2-CH_2-OCH_3\ Cl^{\theta}$ (XXIXA)</p> <p>e.g. firstly XXIXA + strong base secondly add aldehyde thirdly hydrolyse</p> | cf. (P) | cf. (P) | cf. (P) |

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CI is the commercially available compound tri-**O**-acetyl-D-glucal.

The preferred reactions conditions for Reactions AB-AI are:

AB: (1) sodium, methanol, 20°C, 15 minutes; (2) mercuric acetate, 25°C.

5 AC: sodium chloride, sodium borohydride, methanol + isopropanol, 20°C.

AD: triphenylmethyl chloride, pyridine, 35°C.

AE: (1) sodium hydride, tetrahydrofuran, 20°C, (2) 1-(2',4',6'-triisopropylbenzenesulfonyl)imidazole, -30°-20°C.

10 AF: lithium aluminium hydride, methyl t-butyl ether, -10°C.

AG: t-butyldiphenylchlorosilane, imidazole, N,N,dimethyl-formamide, 20°C.

AH: 70% aqueous trifluoroacetic acid, methylene chloride, -80° to -50°C especially -55°C rising over 1 hour to -10° to +10° esp. -10° to 0°, and keeping at latter for 3-5 hours Epimeri-
15 sation can be minimized by employing low temperatures and/or short times and terminating the reaction before completion.

AI: pyridinium chlorochromate or especially chromium trioxide (e.g. as Collins oxidation) in molar excess (e.g. 6 mole per
20 mole of CVIII)/pyridine, pyridine, methylene chloride, 20°-30°C.

AJ: oxidation cf. AI.

AK: reduction cf. a) and S above especially NaBH₄.

25 Resulting compounds may be conventionally separated (e.g. HPLC or column chromatography) or directly further reacted.

The compounds of formulae IVA, IVB, XA, XB, XIA, XVII, XIXA, XXI, XXIIA-XXIID, XXIXA and CI and the reagents not designated by a Roman numeral are known or, if unknown, may be synthesized by processes analogous to those described in the
30 literature for similar known compounds. As for the compound of formula XXV, one isomer is disclosed in Yang et al., Tetrahedron Letters 23, 4305-4308 (1982), another is disclosed in Reaction Scheme III and the synthesis of a third isomer is disclosed in Reaction Scheme III.



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The isomer of Yang et al. and the isomer disclosed in Reaction Scheme III yield lactones having the 4R,6S configuration and, as a result of epimerization in Reaction X, such compounds having the 4R,6R configuration. Lactones having the 4S,6R and 4S,6S configuration may be obtained from the other isomer whose synthesis is disclosed in Reaction Scheme III.

The availability of these intermediates enables synthesis of optically pure end products.

Reaction products both intermediate and final can be isolated and purified in conventional manner whereby intermediates can where appropriately be employed directly in a subsequent reaction

Mixtures of stereoisomers (cis, trans and optical) may be separated by conventional means at whatever stage of synthesis is appropriate. Such methods include re-crystallisation, chromatography, formation of esters with optically pure acids and alcohols or of amides and salts (cf also Sommer et al. J.A.C. S 80, 3271 (1958)) with subsequent reconversion under retention of optical purity. For example diastereoisomeric (-)- α -naphthyl-phenylmethylsilyl derivatives of a lactone type end product of formula I may be separated on a silica column having covalently bound L-phenylglycine (eluant n-hexane/acetate : 1/1).

Salts may be prepared in conventional manner from free acids, lactones and esters and vice-versa. Whilst all salts are covered by the invention pharmaceutically acceptable salts especially sodium, potassium and ammonium particularly sodium salts are preferred.

The various forms of the compounds of formula I are by virtue of their interconvertability useful as intermediates in addition to the use set out below.

Also within the scope of this invention are the intermediates of formulae V, X, XI, XII, XX, XXIV, XXVI-XXVIII and XXIXB-XXIXD. The preferences for each variable are the same as those set forth for the compounds of formula I, with the preferred groups of such compounds including those that correspond to Groups (i)-(xiii) and (xxxix)-lxxxviii) (for



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formulae V, X-XII, XX and XXIXB-XXIXD) and Groups (xiv)-(xx), (xxxiii)-(xxxviii) and (lxxxix)-(cxiv) for formulae XXVI-XXVIII) to the extent consistent therewith.

5 The compounds of formula I possess pharmacological activity in particular they are inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase and as a consequence inhibitors of cholesterol biosynthesis as demonstrated in the following three tests.

10 Test A: In Vitro Microsomal Assay of HMG-CoA Reductase Inhibition:

200 ul. aliquots (1.08-1.50 mg./ml.) of rat liver microsomal suspensions, freshly prepared from male Spargue-Dawley rats (150-225 g. body weight), in Buffer A with 10 mmol. dithiothreitol are incubated with 10 ul. test substance dissolved in dimethylacetamide and assayed for HMG-CoA reductase activity as described by Ackerman et al., J. Lipid Res. 18, 408-413 (1977). In the assay the microsomes are the source of the HMG-CoA reductase enzyme which catalyses the reduction of HMG-CoA to mevalonate. The assay employs a chloroform extraction to separate the product, [^{14}C]mevalonolactone, formed by the HMG-CoA reductase reaction from the substrate, [^{14}C]HMG-CoA. [^3H]mevalono-lactone is added as an internal reference. Inhibition of HMG-CoA reductase is calculated from the decrease in specific activity [$^{14}\text{C}/^3\text{H}$]mevalonate) of test groups compared to controls.

25 Test B: In Vitro Cell Culture Cholesterol Biosynthesis Screen:

30 The cell culture is prepared as follows: Stock monolayer cultures of the Fu5AH rat hepatoma cell line (originally obtained from G. Rothblat; see Rothblat, Lipids 9, 526-535 (1974) are routinely maintained in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% fetal bovine serum (FBS) in 75 cm² tissue culture flasks. For these studies, when the cultures reach



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confluence, they are removed by mild enzymatic treatment with 0.25% trypsin in Hanks' balanced salt solution (without calcium and magnesium). After centrifugation of the cell suspension and aspiration of the enzymatic solution, a cell pellet is

5 resuspended in an appropriate volume of media for seeding into 60 mm. tissue culture dishes. The cultures are incubated at 37°C in an atmosphere of high humidity and 5% carbon dioxide. When the cultures are confluent (approximately 5 days), they are ready for use. The culture media is aspirated from the dishes and

10 replaced with 3 ml of EMEM supplemented with 5 mg/ml of dilipidized serum protein (DLSP) prepared by the method of Rothblat et al., In Vitro 12, 554-557 (1976). Replacement of the FBS with DLSP has been shown to stimulate the incorporation of [¹⁴C]acetate into sterol by removing the exogenous sterol

15 supplied by the FBS, thereby requiring the cells to synthesized sterol. Enhanced 3-hydroxy-3-methylglutaryl Coenzyme A reductase (HMG-CoA reductase) activity is measurable in the cells in response to the lack of exogenous sterol. Following approximately 24 hours incubation at 37°C in the DLSP supplemented media, the

20 assay is initiated by the addition of 3μCi of [¹⁴C]acetate and the test substances solubilized in dimethylsulfoxide (DMSO) or distilled water. Solvent controls and compactin-treated controls are always prepared. Triplicate 60mm. tissue culture dishes are run for each group. After 3 hours incubation at 37°C, the

25 cultures are examined microscopically using an inverted phase contrast microscope. Notations are made of any morphological changes which may have occurred in the cultures. The media is aspirated and the cell layer is gently washed twice with 0.9% sodium chloride solution (saline). The cell layer is then

30 harvested in 3 ml. of 0.9% saline by gentle scraping with a rubber policeman and transferred to a clean glass tube with Teflon lined cap. The dishes are rinsed with 3 ml. of 0.9% saline and rescraped, and the cells are combined with the first harvest. The tubes are centrifuged at 1500 r.p.m. for 10 minutes



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in an IEC PR-J centrifuge, and the supernatant is asperated.

The cells are then extracted as follows: One ml. of 100% ethanol is added to the cell pellet followed by sonication for 10 seconds with a "LO" setting of 50 on a Bronwell Biosonik IV. One
5 hundred ul. are taken for protein determination. One ml. of 15% potassium hydroxide (KOH) is added, and the samples are thoroughly vortexed. Saponification is accomplished by heating the ethanol-KOH treated samples at 60°C for 60 minutes in a water bath. Following dilution of the samples with 2ml. of distilled
10 water, they are extracted three times with 7 ml. of petroleum ether. The petroleum ether extracts are then washed three times with 2 ml. of distilled water and finally taken to dryness under a stream of nitrogen.

The obtained samples are then analyzed by thin layer
15 chromatography (TLC) as follows: Residues from the petroleum ether extraction are taken up in a small volume of hexane and spotted on silica gel 60 TLC plates (E. Merck). Development of the plates is carried out in a 150 parts by volume hexane: 50 parts by volume diethyl ether: 5 parts by volume galcial acetic
20 acid solvent system using a three phase development procedure. Visualization is accomplished in an iodine vapor chamber. The plates are divided into five sections such that each section contains the molecules having the following approximate Rf values: section 1- 0-0.4, section 2- 0.4-0.55, section 3-
25 0.55-0.7, section 4- 0.7-0.9 and section 5- 0.9-1.0. Section 2 contains the non-saponifiable sterols. The five sections of the TLC plates are scraped into scintillation vials. Blanks are also prepared from scrapings of chromatographed non-labelled standards. ACS[®] scintillation cocktail is added, and the
30 radioactivity is determined in a liquid scintillation spectrometer. [¹⁴C]hexadecane standards are used to determine counting efficiencies. The total protein content of the samples is determined employing the Bio-Rad Protein Assay System.



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The results are reported as disintegrations per minute per mg protein (d.p.m./mg protein) for each of the live TLC sections. Mean d.p.m./mg protein \pm standard error of the mean are compared for percentage change (% Δ) and statistical significance with solvent control means. TLC section 2 data is taken as a measure of HMG-CoA reductase activity inhibition.

Test C: In Vivo Cholesterol Biosynthesis Inhibition Tests:
In vivo studies utilize male Wistar Royal Hart rats weighing 150 \pm 20 g which have been kept for 7-10 days on an altered light cycle (6:30 a.m. - 6:30 p.m. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol synthesis at mid-dark, the rats are administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml/100 g body weight. Controls receive vehicle alone. One hour after receiving the test substance, the rats are injected intraperitoneally with about 25 μ Ci/100 g body weight of sodium [1- 14 C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples are obtained under sodium hexobarbital anesthesia and the serum separated by centrifugation.

Serum samples are saponified and neutralized, and the 3 β -hydroxy sterols are precipitated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187, 97 (1950). The [14 C]digitonides are then counted by liquid scintillation spectrometry. After correcting for efficiencies, the results are calculated in nCi (nanocuries) of sterol formed per 100 ml of serum. Inhibition of sterol synthesis is calculated from the reduction in the nCi of sterols formed from test groups compared to controls.

The compounds are thus indicated for use as hypolipoproteinemic and anti-atherosclerotic agents.

An indicated suitable daily dosage for use in the treatment of hyperlipoproteinemia and atherosclerosis is from about



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1 to 2000 mg preferably 1.5 to 100 mg suitably administered in divided dosages of 0.25 to 1000 mg preferably 0.4 to 50 mg two to four times daily or in retard form.

5 The compounds of formula I may be administered in similar manner as known compounds suggested for use in such indications e.g. Compactin. The suitable daily dosage for a particular compound will depend on a number of factors such as its relative potency of activity. It has, for example been determined that the preferred compound (cmpd. no. 13) obtained an IC₅₀ of 9.6
10 nanomolar in test A compared with 0.5 umolar for Compactin. It is therefore indicated that the compounds may be administered at similar or significantly lower dosages than conventionally proposed for Compactin.

15 They may be administered in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form whereby the various forms have activities in the same range.

20 The invention therefore also concerns a method of treating hyperlipoproteinemia or atherosclerosis by administration of a compound of formula I in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form as well as such compounds for use as pharmaceuticals e.g. as hypolipo-
proteinemic and anti-atherosclerotic agents.

25 The compounds may be administered alone, or in admixture with a pharmaceutically acceptable diluent or carrier, and, optionally other excipients, and administered orally in such forms as tablets, elixirs, capsules or suspensions or parenterally in such forms as injectable solutions or suspensions.

30 The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules.

Such compositions also form part of the invention.

35 The following examples, in which all temperatures are in °C illustrate the invention.



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EXAMPLE 1

Methyl (E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-methylindol-2'-yl]hept-6-enoate (Compound no. 1)

a) Ethyl 3-(4'-fluorophenyl)-1-methylindole-2-carboxylate

5 (Reaction Q; compound XVIIa)

To a solution of 8.0 g (28 mmol) of ethyl 3-(4'-fluorophenyl)indole-2-carboxylate in 30 ml of dry dimethylacetamide stirred under nitrogen at -10°, 1.6 g (33 mmol) of sodium hydride is added. The reaction mixture is stirred at -10° under nitrogen
10 for 45 minutes, 4.8 g (32 mmol) of methyl iodide is added at -10°, and the reaction mixture is allowed to warm to room temperature and stirred under nitrogen at room temperature for 2 hours. The reaction mixture is poured into 400 ml of ice/water, neutralized with 4 ml of 2N. hydrochloric acid and extracted
15 several times with diethyl ether. The diethyl ether extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated at reduced pressure. The residue is purified by column chromatography utilizing a silica gel column
20 and chloroform as the eluant. The fractions containing the product are combined and evaporated at reduced pressure, and the residue is crystallized from n-hexane/petroleum ether to obtain the product, m.p. 61-62°.

b) 3-(4'-Fluorophenyl)-2-hydroxymethyl-1-methylindole

25 (Reaction M; compound XVIIIa)

To a solution of 20.0 g (67 mmol) of compound XVIIa in 500 ml of dry tetrahydrofuran stirred at -78° under nitrogen, 80 ml of 25% (by weight) diisobutylaluminum hydride/toluene is added, and the reaction mixture is stirred at -78° under nitrogen for 4
30 hours. The reaction mixture is allowed to warm to -10°, an additional 30 ml of 25% (by weight) diisobutylaluminum hydride/toluene is added, the reaction mixture is stirred at 0° under nitrogen for an additional 3 hours, a further 30 ml of 25% (by



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weight) diisobutylaluminum hydride/toluene is added, and the reaction mixture is stirred at 0° under nitrogen for a further 1 hour. The reaction mixture is treated with saturated ammonium chloride solution and filtered, and the organic layer is separated, dried over anhydrous magnesium sulfate, filtered and evaporated at reduced pressure. The residue is triturated with n-hexane to obtain the product, m.p. 99°-104°.

c) 3-(4'-Fluorophenyl)-1-methylindole-2-carboxaldehyde
(Reaction N; compound IVa)

A mixture of 17.0 g (67 mmol) of compound XVIIIa, 90.0 g (1.03 mol) of manganese dioxide and 1.2 l of anhydrous diethyl ether is stirred at room temperature under nitrogen for 14 hours. The reaction mixture is filtered, and the diethyl ether is evaporated at reduced pressure. The residue is flash chromatographed on a silica gel column using methylene chloride as the eluant, the fractions containing the product are combined and evaporated at reduced pressure, and the residue is triturated with n-pentane to obtain the product, m.p. 75°-79°.

d) (E)-3-[3'-(4"-Fluorophenyl)-1'-methylindol-2'-yl]propenaldehyde (Reaction O; compound IVb)

25 ml of 1.7M. n-butyl lithium/n-hexane (42 mmol) is added dropwise to a solution of 14.5 g (40 mmol) of tri-n-butylstannyl-vinylethoxide in 600 ml of dry tetrahydrofuran stirred at -78° under nitrogen, stirring is maintained for 2 hours under the same conditions, and 9.0 g (35.6 mmol) of compound IVa dissolved in 60 ml of dry tetrahydrofuran, is added rapidly dropwise. The reaction mixture is stirred at -78° under nitrogen for 3.5 hours, quenched with 60 ml of saturated ammonium chloride solution and extracted several times with diethyl ether. The diethyl ether extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated at reduced pressure. The residue is partitioned between n-hexane and acetonitrile (to remove the organotin compounds), and the acetonitrile layer is



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evaporated at reduced pressure to obtain an oil. The oil is dissolved in 300 ml of tetrahydrofuran, 50 ml of water and 30 mg of p-toluenesulfonic acid monohydrate are added, and the reaction mixture is stirred for 2 hours at room temperature and then extracted several times with diethyl ether. The diethyl ether extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness at reduced pressure. The residue is triturated with n-hexane/diethyl ether to obtain the product, m.p. 110°-112°. A subsequent batch melted at 115-118°.

e) Methyl (E)-7-[3'-(4"-fluorophenyl-1'-methylindol-2'-yl)]-5-hydroxy-3-oxohept-6-enoate (Reaction A; compound Va)

3.5 ml (32.4 mmol) of methyl acetoacetate is added dropwise to a suspension of 1.6 g of 50% (by weight) sodium hydride (33.3 mmol) in 400 ml of dry tetrahydrofuran stirred at -15° under nitrogen. The reaction mixture is stirred at -15° under nitrogen for 20 minutes, 19 ml of 1.7M. n-butyl lithium/n-hexane (31.9 mmol) is added, the reaction mixture is stirred at -15° under nitrogen for 20 minutes, a solution of 5.3 g (19 mmol) of compound IVb in 100 ml of dry tetrahydrofuran is added, and the reaction mixture is stirred at -15° under nitrogen for 30 minutes. The reaction mixture is quenched with dilute hydrochloric acid and extracted several times with diethyl ether. The diethyl ether extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness at reduced pressure. The residue is triturated with n-pentane (to remove excess methyl acetoacetate) to obtain the crude product as an oil.

The product is a racemate that may be resolved into its d and l components.



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f) Methyl (E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-methyl-indol-2'-yl]-hept-6-enoate (process a); compound no. 1)

2.0 g of borane-t-butylamine complex is added to a solution of 8.0 g (20.2 mmol) of crude racemic compound Va in 200 ml of absolute ethanol stirred at 0° under nitrogen. The reaction mixture is stirred at 0° under nitrogen for 3 hours, and saturated sodium chloride solution is added. The reaction mixture is acidified with dilute hydrochloric acid and extracted several times with diethyl ether. The diethyl ether extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness at reduced pressure. The obtained oil is purified by flash chromatography using a silica gel column and 1:1 ethyl acetate/chloroform as the eluant. The product, a mixture of four stereoisomers, is obtained as a yellow oil.

The obtained mixture of stereoisomers (erythro and threo) may be separated by conventional means into two racemic mixtures each of which may be resolved into two optically pure enantiomers. The four isomers may be designated as the 3R,5R, 3S,5S, 3R,5S and 3S,5R isomers. Preferred are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, viz., the 3R,5R-3S,5S and the 3R,5S-3S,5R racemate.

EXAMPLE 2

25 (E)-3,5-Dihydroxy-7-[3'-(4"-fluorophenyl)-1'-methylindol-2'-yl]-hept-6-enoic acid (process d)/ester hydrolysis; compound no. 3)

2.8 ml of 1N. aqueous potassium hydroxide (2.8 mmol) is added to a solution of 1.1 g (2.77 mmol) of compound no. 1 in 100 ml of 95% aqueous methanol stirred at room temperature, and the reaction mixture is stirred at room temperature for 3 hours. The solvent is evaporated at reduced pressure, the residue [crude potassium salt (compound 2) a mixture of four stereoisomers] is dissolved in water, and the aqueous



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solution is extracted with diethyl ether. The aqueous phase is acidified with dilute hydrochloric acid (pH 6.0) and extracted several time with diethyl ether. The diethyl ether extracts are combined, washed with water, washed with saturated sodium
5 chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated at reduced pressure to give the crude product as a yellow oil. It is a mixture of four stereoisomers.

If desired, potassium salt or free acid (compound no. 3) may be separated into two racemic mixtures (erythro, threo) each
10 of which may be resolved into two optically pure enantiomers. The four stereoisomers may be designated as the 3R,5R, 3S,5S, 3R,5S and 3S,5R isomers. Preferred are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, viz., the 3R,5R-3S,5S racemate and the 3R,5S-3S,5R racemate.

15 EXAMPLE 3

(E)-6-[3'-(4"-Fluorophenyl)-1'-methylindol-2'-ylethenyl]-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (process e)/lactonisation; compound 4)

a) A solution of 1.1 g (2.87 mmol) of crude compound no. 3
20 in 50 ml of dry benzene is refluxed for 8 hours. The solvent is evaporated at reduced pressure, and the residue is flash chromatographed on a silica gel column utilizing 19:1 chloroform/methanol as the eluant to obtain the product as a mixture of four diastereoisomers (two cis and two trans)(compound 4).

25 bi) The mixture of isomers obtained is separated by high pressure liquid chromatography using a silica gel column and, as the solvent, 7:2:1 methyl t-butyl ether/n-hexane/acetone to obtain the racemic trans compound m.p. 147-150° (compound no. 5). A subsequent batch melted at 150-154°.

30 bii) The obtained trans racemate may be resolved by conventional means into two optically pure enantiomers, the 4R,6S and 4S,6R isomers by, for example, (i) reacting with (-)- α -naphthylphenylmethychlorosilane, (ii) separating the obtained



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diastereoisomeric silyloxy compounds and (iii) cleaving the silyl groups with tetra-n-butylammonium fluoride in a mixture of acetic acid and tetrahydrofuran, as set forth above. The amorphous solid 4R,6S enantiomer has an $[\alpha]^{25} = -18.5^\circ$ (CHCl_3 , $c = 0.2$ g
5 (compound 17). The 4S,6R enantiomer was also an amorphous solid.

c) The racemic cis lactone may also be isolated from the silica gel column, m.p. $48^\circ\text{--}62^\circ\text{C}$ (dec.) (compound 6). It too may be resolved by conventional means into two optically pure enantiomers. The two stereoisomers may be designated at the 4R,6R
10 and 4S,6S isomers, the former being preferred.

EXAMPLE 4

Methyl (+)-erythro-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]hept-6-enoate (compound no. 7)

15 a) (E)-3-[3'-(4"-Fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]-prop-2-enal (Reaction AA; compound IVc)

A solution of 50 ml (49.6 g, 0.5 mole) of 3-N,N-dimethyl-aminoacrolein in 200 ml of dry acetonitrile is slowly added over a 30 minute period to a solution of 50 ml (82.5 g, 0.5392 mole) of phosphorus oxychloride in 200 ml of dry acetonitrile stirred
20 at $-10^\circ\text{--}0^\circ$ under nitrogen. 45.3 g (0.1788 mole) of 3-(4'-Fluorophenyl)-1-(1'-methylethyl)indole (XXIIAa) is added portionwise over a 2 minute period to the reaction mixture stirred at $0^\circ\text{--}5^\circ$. The reaction mixture is refluxed for 24 hours under nitrogen, cooled to room temperature and slowly poured (over a 20 minute
25 period) into a cold (10°) stirred mixture of 2 litres of toluene and a solution of 130 g of sodium hydroxide in 2 litres of water so that the temperature does not exceed 26° . The reaction mixture is filtered to remove the insolubles, and the toluene layer is separated and washed twice with 1 litre portions of water. The
30 additional insolubles are removed by filtration, and the toluene layer is evaporated at reduced pressure and $50^\circ\text{--}60^\circ$. The obtained viscous oil is chromatographed on 550 g of silica gel (20-230 mesh A.S.T.M.) using methylene chloride as the eluant; twenty



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100 ml fractions are collected over a 2 hour period. The fractions containing the desired product (as determined by thin layer chromatography) are combined and evaporated to dryness at reduced pressure and 50°-60° to obtain the crude solid product.

5 The crude product is dissolved in 70 ml of refluxing absolute ethanol, the obtained solution is cooled to 65°, 70 ml of n-heptane is added, and the resulting solution is cooled to -5°-0° for 15 minutes. The precipitate solids are collected by filtration, washed with 20 ml of ice cold n-heptane and vacuum

10 dried at 50°-55° to obtain the yellow product m.p. 122°-123°. A subsequent batch melted at 129-132°.

3-(4'-Fluorophenyl)-1-(1'-methylethyl)indole (m.p. 94.5-95°) is prepared via 4-chloroacetyl-1-fluorobenzene and N-(4-fluorobenzoylmethyl)-N-(1-methylethyl)aniline (m.p. 78-81°) in conventional manner.

15

b) Methyl (+)-(E)-7-[3'-4"-fluorophenyl)-1'-(1"-methylethyl)-indol-2'-yl]-5-hydroxy-3-oxohept-6-enoate (Reaction A; compound Vb)

Analogous to 1e) m.p. 95-97°.

20 The product is a racemate which may be resolved into its R and S components.

c) Methyl (+)-erythro-(E)-3,5-dihydroxy-7-[3'(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'yl]hept-6-enoate Process a)/ stereospecific; compound no. 7)

25 (i) 30 ml of 1M. triethylborane/tetrahydrofuran (30 mmol) is added dropwise to a solution of 12.2 g (26 mmol assuming 100% yield) of crude Compound Vb in 400 ml of dry tetrahydrofuran (distilled over lithium aluminium hydride) stirred at room temperature, 55 ml of air (at 760 mm Hg and 25°) is bubbled

30 through over 5 minutes, and the reaction mixture is stirred at room temperature under nitrogen for 2 hours. The reaction mixture is cooled to -80°, 1.3 g (34 mmol) of sodium borohydride is added, and the reaction mixture is stirred overnight at -80°



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under nitrogen. The reaction mixture is allowed to warm to
-10°-0°, quenched by the dropwise addition of sufficient 2N.
hydrochloric acid to lower the pH to 2 and extracted with diethyl
ether. The diethyl ether extract is washed twice with saturated
5 sodium chloride solution, dried over anhydrous magnesium sulfate
and evaporated at reduced pressure to a yellow oil, the crude
ethylborate ester. 400 ml of anhydrous methanol is added, and the
reaction mixture is stirred at room temperature for 2.5 hours.
The methanol is evaporated at reduced pressure and 40°, and the
10 residue is dissolved in 4:1 (by volume) chloroform/ethyl acetate
and chromatographed on a silica gel column using the same solvent
as the eluant. The fractions containing the relatively pure
product are combined and evaporated at reduced pressure to obtain
the product as an oil.

15 (ii) An impure chromatography fraction (containing some
product) is evaporated at reduced pressure, and the residue is
trituated with diethyl ether and n-pentane and seeded with a
crystal that formed upon addition of the methanol to the
ethylborate ester to obtain the product (96% erythro) as a white
20 powder, m.p. 122°-124°.

The product is a racemate which may be resolved into two
optically pure enantiomers, the 3R,5S and 3S,5R isomers, of which
the former is preferred.

EXAMPLE 5

25 Erythro-(+)-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-
methylethyl)indol-2'-yl]hept-6-enoic acid (process d)/esterhydro-
lysis; compound no. 8)

(a) 4.5 ml of 1N. sodium hydroxide solution (4.5 mmol) and
2.0 g (4.7 mmol) of Compound 7 are stirred in 150 ml of ethanol
30 at room temperature for 2 hours, the solvent is evaporated at
reduced pressure, and the residue is dissolved in 50 ml of
water. The aqueous solution is gently extracted with diethyl
ether, the traces of ether in the aqueous layer are removed at



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reduced pressure, and the aqueous layer is freeze dried to obtain the racemic product as its sodium salt (compound no. 9) m.p. 194°-197°.

5 (b) Compound no. 9 is dissolved in water, and the solution is acidified to pH2 with 2N. hydrochloric acid and extracted with diethyl ether. The diethyl ether extract is washed three times with saturated sodium chloride solution, dried over anhydrous magnesium sulfate and evaporated at reduced pressure to obtain the crude solid racemic free acid (compound no. 8).

10 Sodium salt and free acid can be resolved into their 3R,5S and 3S,5R isomers the former being preferred.

EXAMPLE 6

15 (E)-(+)-4-hydroxy-6-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)-indol-2'-ylethenyl]-3,4,5,6-tetrahydro-2H-pyran-2-one (process e)/catalyzed lactonisation; compound no. 10)

6.9 g of crude Compound no. 8 (which contains some threo isomer) and 7 g of N-cyclohexyl-N'-[2-(N"-methylmorpholinium)ethyl]carbodiimide p-toluenesulfonate are stirred in 300 ml of methylene chloride at 20 room temperature for 3 hours. The reaction mixture is extracted with water, dried over anhydrous magnesium sulfate and evaporated at reduced pressure. The residual oil (containing compound no. 10) is chromatographed on a silica gel column utilizing 7:2:1 (by volume) methyl t-butyl ether:n-hexane:acetone as the eluant. The 25 initial fractions, containing the racemic trans lactone, are combined and evaporated at reduced pressure to obtain the product as a foam (compound no. 11). Fractions containing the cis compound are evaporated at reduced pressure to obtain a solid product m.p. 170-175° (dec.) (compound no. 12).

30 The trans and cis products are racemates which may be resolved into their 4R,6S and 4S,6R or 4R,6R, 4S,6S isomers respectively, the former being preferred in each case.

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EXAMPLE 7

Sodium erythro-(+)-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]hept-6-enoate (alternative method/process d)/lactone hydrolysis; compound no. 13 = compd. 9)

5 2.6 g of the corresponding trans lactone (cf. Ex. 6), 12.6 ml of 0.5N. sodium hydroxide solution (6.3 mmol) and 200 ml of absolute ethanol are stirred for 2 hours at room temperature, the solvent is evaporated at reduced pressure, and the residue is dissolved in 150 ml of water. The aqueous solution is gently
10 washed with diethyl ether and freeze dried to obtain the solid racemic product. This compound can be resolved into its optically pure isomers 3R,5S ($[\alpha]^{25} = -13.33^\circ$ (CHCl₃, c = 0.99 g); compound no. 14) and 3S,5R (compound no. 15) the former being preferred.

15 The 3R,5S isomer can also be obtained by the above process directly from the optically pure compound 20.

EXAMPLE 8

Sodium threo-(+)-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]hept-6-enoate (compound no. 16)

20 Obtained analogously to Example 7 from the corresponding cis lactone.

This compound may also be resolved into its optically pure isomers 3R,5S and 3S,5R, whereby the former is preferred.

EXAMPLE 9

25 (E)-Trans-6S-[3'-(4"-fluorophenyl)-1'-methylindol-2'-ylethenyl]-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (compound no. 17)

a) 3-(4'-Fluorophenyl)-1-methylindole-2-carboxaldehyde (Reaction R; compound no. IVd)

30 78.5 ml (0.84 mole) of phosphorus oxychloride is added dropwise over a 20 minute period to 213 ml of dimethylformamide stirred at 0° under nitrogen, the temperature of the reaction mixture not being allowed to exceed 10°. The reaction mixture is heated to 80°, a solution of 163.5 g (0.727 mole) of 3-(4'fluorophenyl)-1-methylindole in 270 ml of dimethylformamide is added at a rate such that the temperature of the reaction mixture is



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maintained at 81°-83°, the reaction mixture is maintained at 80°-81° for 5 hours and cooled to 10°, and 1 litre of 15% sodium hydroxide solution is added dropwise at a rate such that the temperature of the reaction mixture is maintained at 35°-40°, the reaction mixture being stirred under nitrogen throughout. The reaction mixture is cooled to 25°, and the solids are collected by filtration, washed three times with 500 ml portions of water and dissolved in 500 ml of methylene chloride. The methylene chloride solution is filtered through 500 ml of silica gel (70-230 mesh A.S.T.M.) and the silica gel is carefully washed with 2 litres of methylene chloride. The methylene chloride solutions are combined and concentrated to a volume of 300 ml at reduced pressure, 300 ml of absolute ethanol is added and the reaction mixture is distilled until the internal temperature reaches 78°. The reaction mixture is cooled to 0° and the precipitated bright yellow product is collected by filtration and vacuum dried at room temperature, m.p. 80.5°-81.5°.

b) 3-(4'-Fluorophenyl)-2-hydroxymethyl-1-methylindole
(Reaction S; compound XVIIIa)

A solution of 160 g (0.6324 mole) of Compound IVd in 650 ml of tetrahydrofuran is added over a 20 minute period to a mixture of 9.6 g (0.25 mole) of sodium borohydride, 650 ml of tetrahydrofuran and 65 ml of methanol stirred at 0° under nitrogen, the temperature of the reaction mixture not being allowed to exceed 14°. The reaction mixture is stirred under nitrogen at 5°-10° for 30 minutes, and the tetrahydrofuran and methanol are distilled at atmospheric pressure. 1 litre of toluene is added to the oily residue (200-300 ml) and the residual tetrahydrofuran is distilled at atmospheric pressure until the temperature reaches 108°-110°. The toluene solution is cooled to 40°, 1.3 litre of 0.5N. sodium hydroxide is rapidly added, and the two phases are mixed and separated. The organic phase is heated to 50°-55°, 1.1 litre of n-hexane is added, the

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the solution is cooled to 5°, and the precipitated colourless product is collected by filtration and vacuum dried for 16 hours at room temperature, m.p. 110°-111°.

5 c) 2-Chloromethyl-3-(4'-fluorophenyl)-1-methylindole
 (Reaction T; compound XXIIIa)

29.5 ml (0.404 mole) of thionyl chloride is added over a 10 minute period to a solution of 63.8 g (0.25 mole) of Compound XVIIIa in 650 ml of dry tetrahydrofuran (dried over molecular sieves) stirred at -7° under nitrogen. The reaction mixture is
10 stirred at -5°-0° under nitrogen for 2.5 hours, 350 ml toluene is added (with cooling to keep the temperature of the reaction mixture at or below 5°, tetrahydrofuran and excess thionyl chloride are distilled at 0.5-2 mm. Hg. and 0°-10° until the volume of the reaction mixture is about 400 ml, an additional
15 350 ml of toluene is added and another 100 ml of solvent is distilled at 0.5-1 mm. Hg. and 10°-20° to obtain a solution of the product in toluene.

 d) 3-(4'Fluorophenyl)-1-methyl-2-triphenylphosphonium-
 methylindole chloride (Reaction V; compound XXIVa)

20 A solution of 66.2 g (0.25 mole) of triphenylphosphine in 1 litre of toluene is added over a 3 minute period to the solution obtained in c), stirred at 15°-20° under nitrogen, and the reaction mixture is stirred at 108°-110° under nitrogen for 5 hours and cooled to 25°. The product is collected by filtration,
25 washed twice with 50 ml portions of toluene and once with 50 ml of n-heptane and vacuum dried, m.p. 270°-271° (dec.).

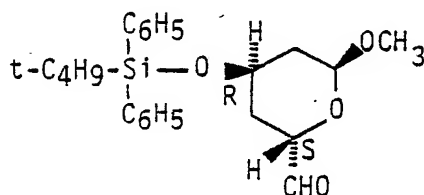
 e) (E)-4BR-(1',1'-dimethylethyl-diphenylsilyloxy)-6αS-
 [3'-(4"-fluorophenyl)-1'-methylindol-2'-ylethenyl]-2β-
 methoxy-3,4,5,6-tetrahydro-2-pyran and the corresponding
30 (Z) form (Reaction W; compounds XXVIa and XXVIb)

6.0 ml of 1.3M n-butyllithium/n-hexane (7.8 mmol) is added dropwise over a 7 minute period to a slurry of 4.0 g (7.47 mmol) of Compound XXIVa stripped from toluene at reduced pressure and



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dried under high vacuum prior to use in 100 ml of dry tetrahydrofuran (freshly distilled from sodium and benzophenone) stirred at room temperature under nitrogen. The reaction mixture is cooled to 0°, and 2.98 g (7.48 mmol) of compound



(stripped from toluene at reduced pressure and dried under high vacuum prior to use) in 20 ml of dry tetrahydrofuran is added dropwise over a 5 minute period, an additional 10 ml of dry tetrahydrofuran is added, and the reaction mixture is maintained at about 0° for 45 minutes; allowed to warm to room temperature and maintained at room temperature for 17 hours, the reaction mixture being stirred under nitrogen throughout. The reaction mixture is poured into 500 ml of water and extracted four times with 250 ml portions of diethyl ether. The diethyl ether extracts are combined and dried over anhydrous magnesium sulfate and then over anhydrous sodium sulfate and evaporated at reduced pressure. The last traces of diethyl ether are removed under high vacuum to obtain a semi-solid residue. The residue is subjected to medium pressure liquid chromatography utilizing a silica gel column and methylene chloride as the eluant, with those fractions containing one product and one or more contaminants or a mixture of the products (with or without one or more contaminants) as determined by thin layer chromatography being recycled, to obtain the (E) (i.e., trans) olefin (Compound XXVIa) as an orange foam and the (Z) (i.e., cis) olefin (Compound XXVIb) also as an orange foam.

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f) (E)-4BR (1',1'-dimethylethyl-diphenylsilyloxy)-6 α S-
[3'-(4"-fluorophenyl)-1'-methylindol-2'-ylethenyl]-2-
hydroxy-3,4,5,6-tetrahydro-2H-pyran; compound XXVIIa and
its 6BR isomer; compound XXVIIb (Reaction X)

5 1.18 g (1.9 mmol) of compound XXVIa is dissolved in 56 ml
of glacial acetic acid, 37.2 ml of tetrahydrofuran is added, and
18.6 ml of distilled water is slowly added, the reaction mixture
being stirred at room temperature throughout. The reaction
mixture is stirred at 60° for 18.5 hours and allowed to cool. The
10 tetrahydrofuran is evaporated at reduced pressure, and the
reaction mixture is poured into 500 ml of distilled water and
extracted four times with 300 ml portions of diethyl ether. The
diethyl ether extracts are combined, washed with saturated sodium
bicarbonate solution (until no gas is evolved upon shaking),
15 dried over anhydrous magnesium sulfate and then over anhydrous
sodium sulfate and evaporated to dryness at reduced pressure. The
last traces of solvent are removed under high vacuum to obtain a
yellow foam. Flash chromatography of the foam utilizing 250 g of
silica gel and 1:1 (by volume) diethyl ether/n-hexane as the
20 eluant yielded Compound XXVIIa and Compound XXVIIb.

g) (E)-4BR-(1',1'-dimethylethyl-diphenylsilyloxy)-6 α S-[3'-
(4"-fluorophenyl)-1'-methylindol-2'-ylethenyl]-3,4,5,6-
tetrahydro-2H-pyran-2-one (Reaction Y; compound XXVIIIa)

A solution of 236.8 mg (0.391 mmol) of compound XXVIIa in 8
25 ml of acetone (passed through a column of Activity I alumina
immediately prior to use) is added to 137.5 mg (1.174 mmol) of
N-methylmorpholine N-oxide (obtained by heating N-methylmorpho-
line N-oxide hydrate at 90° for 2-3 hours under high vacuum), the
reaction mixture is stirred at room temperature under nitrogen
30 until the solid dissolves, 23.5 mg (0.025 mmol) of
dichlorotris(triphenylphosphine)ruthenium (II) is added, and the
reaction mixture is stirred under nitrogen for 55 minutes, 10 ml
of diethyl ether is added, and the resulting solid is washed



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several times with diethyl ether. The diethyl ether washings are combined, the diethyl ether is evaporated at reduced pressure to near dryness, and the residue is dissolved in 100 ml of diethyl ether. The diethyl ether solution is washed twice with 100 ml portions of ice-cold 2.5% hydrochloric acid, twice with 100 ml portions of saturated sodium bicarbonate solution and once with 100 ml of saturated sodium chloride solution, dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure to obtain the crude product as a yellow oil.

h) (E)-trans-6S-[3'-(4"-fluorophenyl)-1'-methylindol-2'-yl-ethenyl]-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one
(Process d)/deprotection; compound no. 17)

113 μ l of glacial acetic acid is added dropwise to a solution of 237.5 mg (0.391 mmol) of crude Compound XXVIIIa in 18 ml of dry tetrahydrofuran stirred at room temperature under nitrogen followed by the dropwise addition of 1.564 ml of 1M. tetra-n-butylammonium fluoride/tetrahydrofuran. The reaction mixture is stirred at room temperature under nitrogen for 2 hours, poured into 200 ml of ice-cold water and extracted four times with 75 ml portions of diethyl ether. The organic phase are combined, washed once with 300 ml of saturated sodium bicarbonate solution and once with 300 ml of saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent is evaporated at reduced pressure, with the last traces being evaporated under high vacuum to obtain a yellow oil which is triturated with diethyl ether to obtain the product as a pale yellow solid. Additional product is obtained from the mother liquor by repeating this procedure three times, m.p. 139°-140°.

A second batch obtained by resolution of the racemate had an $[\alpha]_D^{25} = -18.5^\circ$ (CHCl₃, c=0.2 g) [(cf. Example 3)b)ii)].

The corresponding (E), cis, 6R,4R isomer is obtained analogously (compound no. 18) starting from compound XXVIIb.



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The corresponding (Z), trans, 6S,4R isomer is obtained analogously; compound no. 19

$[\alpha]_D^{25} = +136.935^\circ$ (CH₂Cl₂, c = 1.24 g) starting from XXVib.

5 EXAMPLE 10

(E)-Trans-6S-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)-indol-2'-ylethenyl]-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (compound no. 20)

Obtained analogously to Example 9 starting from XXIIAa and the lactone illustrated in Example 9e).

$[\alpha]_D^{25} = -15.84^\circ$ (CHCl₃, c = 1.3 g).

Compounds 1 to 20 have the following structures:

Compound no. 1: R = 4-F-C₆H₄-; R₀ = CH₃; R₂ = R₃ = H; X = (E)CH=CH; Z = IIa; R₆ = H; R₇ = CH₃ (mixture of 4 stereoisomers).

15 Compound no. 2: R = 4-F-C₆H₄-; R₀ = CH₃; R₂ = R₃ = H; X = (E)CH=CH; Z = IIa; R₆ = H; R₇ = K (mixture of 4 stereoisomers).

Compound no. 3: R = 4-F-C₆H₄-; R₀ = CH₃; R₂ = R₃ = H; X = (E)CH=CH; Z = IIa; R₆ = R₇ = H (mixture of 4 stereoisomers).

20 Compound no. 4: R = 4-F-C₆H₄-; R₀ = CH₃; R₂ = R₃ = H; X = (E)CH=CH; Z = IIb; R₆ = H (mixture of 4 stereoisomers).

Compound no. 5: R = 4-F-C₆H₄-; R₀ = CH₃; R₂ = R₃ = H; X = (E)CH=CH; Z = IIb; R₆ = H (trans racemate).

Compound no. 6: R = 4-F-C₆H₄-; R₀ = CH₃; R₂ = R₃ = H; X = (E)CH=CH; Z = IIb; R₆ = H (cis racemate).

25 Compound no. 7: R = 4-F-C₆H₄-; R₀ = i-C₃H₇; R₂ = R₃ = H; X = (E)CH=CH; Z = IIa; R₆ = H; R₇ = CH₃ (erythro racemate).

Compound no. 8: R = 4-F-C₆H₄-; R₀ = i-C₃H₇; R₂ = R₃ = H; X = (E)CH=CH; Z = IIa; R₆ = R₇ = H (erythro racemate).

30 Compound no. 9 (= compd. no. 13): R = 4-F-C₆H₄-; R₀ = i-C₃H₇; R₂ = R₃ = H; X = (E)CH=CH; Z = IIa; R₆ = H; R₇ = Na (erythro racemate).

Compound no. 10: R = 4-F-C₆H₄-; R₀ = i-C₃H₇; R₂ = R₃ = H; X = (E)CH=CH; Z = IIb; R₆ = H (mixture of 4 stereoisomers).



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- Compound no. 11: R = 4-F-C₆H₄-; R₀ = i-C₃H₇; R₂ = R₃ = H;
X = (E)CH=CH; Z = IIb; R₆ = H (trans racemate).
- Compound no. 12: R = 4-F-C₆H₄-; R₀ = i-C₃H₇; R₂ = R₃ = H; X =
(E) CH=CH; Z = IIb; R₆ = H (cis racemate).
- 5 Compound no. 13 (= compd. no. 9).
- Compound no. 14: R = 4-F-C₆H₄-; R₀ = i-C₃H₇; R₂ = R₃ = H; X =
(E)CH=CH; Z = IIa; R₆ = H; R₇ = Na (erythro/3R,5S isomer).
- Compound no. 15; R = 4-F-C₆H₄-; R₀ = i-C₃H₇; R₂ = R₃ = H; X =
(E)CH=CH; Z = IIa; R₆ = H; R₇ = Na (erythro 3S,5R isomer).
- 10 Compound no. 16: R = 4-F-C₆H₄-; R₀ = i-C₃H₇; R₂ = R₃ = H; X =
(E)CH=CH; Z = IIa; R₆ = H; R₇ = Na (threo racemate).
- Compound no. 17: R = 4-F-C₆H₄-; R₀ = CH₃; R₂ = R₃ = H; X =
(E)CH=CH; Z = IIb; R₆ = H (trans/6S,4R isomer).
- Compound no. 18; R = 4-F-C₆H₄-; R₀ = CH₃; R₂ = R₃ = H; X =
15 (E)CH=CH; Z = IIb; R₆ = H (cis/6R,4R isomer).
- Compound no. 19: R = 4-F-C₆H₄-; R₀ = CH₃; R₂ = R₃ = H; X =
(Z)CH=CH; Z = IIb; R₆ = H (trans/6S,4R isomer).
- Compound no. 20: R = 4-F-C₆H₄-; R₀ = i-C₃H₇; R₂ = R₃ = H; X =
(E)CH=CH; Z = IIb; R₆ = H (trans/6S,4R isomer).
- 20 The compounds of the following tables may be prepared
analogously to the preceding examples or according to processes
set out hereinbefore.

[Abbreviations: DB = direct bond

D = mixture of diastereoisomers
(four stereoisomers)

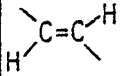
E = erythro racemate
(two stereoisomers)

T = threo racemate
(two stereoisomers)]

TABLE I

(Compounds of type IAa: $R_6 = H$; when only one substituent or H appears in column " R_5 , R_{5a} " then $R_{5a} = H$)

| | Cmpd. No. | R_1 | R_2 | R_3 | R_4 | R_5 , R_{5a} | X | R_7 | Isomer(s) | m.p. |
|----|-----------|---------------------------------|--|-------|-------------------|---------------------|----|-------------------------------|-----------|-----------------|
| 5 | 21 | CH ₃ | H | H | H | H | | CH ₃ | D | |
| | 22 | CH ₃ | H | H | H | H | " | C ₂ H ₅ | D | Viscous oil |
| | 23 | CH ₃ | H | H | H | H | " | Na | D | |
| | 24 | CH ₃ | H | H | H | H | " | H | D | |
| | 25 | CH ₃ | H | H | H | H | " | Na | E | Amorphous solid |
| 10 | 26 | CH ₃ | H | H | H | H | " | Na | T | Amorphous solid |
| | 27 | CH ₃ | 6-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | C ₂ H ₅ | D | Solid foam |
| | 28 | CH ₃ | 6-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | K | D | |
| | 29 | CH ₃ | 6-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | Na | D | Amorphous solid |
| | 30 | CH ₃ | 6-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | H | D | |
| 15 | 31 | CH ₃ | H | H | 4-F | H | DB | CH ₃ | D | |
| | 32 | CH ₃ | H | H | 4-F | H | DB | Na | D | |
| | 33 | CH ₃ | H | H | 4-F | H | DB | H | D | |
| | 34 | CH ₃ | H | H | 3-CH ₃ | 4-CH ₃ | | C ₂ H ₅ | D | Oil |
| | 35 | CH ₃ | H | H | 3-CH ₃ | 4-CH ₃ | " | K | D | |
| 20 | 36 | CH ₃ | H | H | 3-CH ₃ | 4-CH ₃ | " | H | D | |
| | 37 | i-C ₃ H ₇ | H | H | 4-F | H | " | C ₂ H ₅ | D | |
| | 38 | " | H | H | 4-F | H | " | CH ₃ | D | Viscous oil |
| | 39 | " | H | H | 4-F | H | " | K | D | |
| | 40 | " | H | H | 4-F | H | " | H | D | |
| 25 | 41 | CH ₃ | 4-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | C ₂ H ₅ | D | Viscous oil |
| | 42 | CH ₃ | 4-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | K | D | |
| | 43 | CH ₃ | 4-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | H | D | |
| | 44 | CH ₃ | H | H | 3-CH ₃ | 5-CH ₃ | " | C ₂ H ₅ | D | Viscous oil |
| | 45 | CH ₃ | H | H | 3-CH ₃ | 5-CH ₃ | " | K | D | |
| 30 | 46 | CH ₃ | H | H | 3-CH ₃ | 5-CH ₃ | " | H | D | |
| | 47 | CH ₃ | H | H | 3-CH ₃ | 5-CH ₃ | " | Na | E | Amorphous solid |
| | 48 | CH ₃ | H | H | 3-CH ₃ | 5-CH ₃ | " | Na | T | Amorphous solid |

| Cmpd. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ , R _{5a} | X | R ₇ | Isomer(s) | m.p. |
|-----------|--|--|-------------------|-------------------|-------------------------------------|--|-------------------------------|-----------|---------------------|
| 49 | CH ₃ | 5-Cl | H | 4-F | H |  | C ₂ H ₅ | D | 96°-105° |
| 50 | CH ₃ | 5-Cl | H | 4-F | H | " | K | D | |
| 51 | CH ₃ | 5-Cl | H | 4-F | H | " | H | D | |
| 52 | CH ₃ | 5-OCH ₃ | H | 4-F | H | " | C ₂ H ₅ | D | Viscous oil |
| 53 | CH ₃ | H | H | 4-F | H | " | Na | E | 193°-196° (dec.) |
| 54 | CH ₃ | 7-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | C ₂ H ₅ | D | 78°-82° |
| 55 | CH ₃ | 7-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | Na | E | Amorphous solid |
| 56 | CH ₃ | 7-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | Na | T | Amorphous solid |
| 57 | CH ₃ | 5-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | C ₂ H ₅ | D | Viscous oil |
| 58 | C ₆ H ₅ -CH ₂ CH ₂ | H | H | 4-F | H | " | CH ₃ | D | Oil |
| 59 | C ₆ H ₅ -CH ₂ CH ₂ | H | H | 4-F | H | " | Na | E | Amorphous solid |
| 60 | C ₂ H ₅ | H | H | 4-F | H | " | C ₂ H ₅ | D | Viscous oil |
| 61 | C ₂ H ₅ | H | H | 4-F | H | " | Na | E | Amorphous solid |
| 62 | C ₂ H ₅ | H | H | 4-F | H | " | Na | T | Amorphous solid |
| 63 | i-C ₃ H ₇ | 4-CH ₃ | 6-CH ₃ | 4-F | H | " | C ₂ H ₅ | D | 107°-110° |
| 64 | " | 4-CH ₃ | 6-CH ₃ | 4-F | H | " | Na | E | Solid foam |
| 65 | " | 4-CH ₃ | 6-CH ₃ | 4-F | H | " | Na | T | Solid foam |
| 66 | " | H | H | 3-CH ₃ | 5-CH ₃ | " | CH ₃ | D | Viscous oil |
| 67 | " | H | H | 3-CH ₃ | 5-CH ₃ | " | Na | E | 183°-186° |
| 68 | " | 5-cyclohexyl | H | 4-F | H | " | CH ₃ | D | Viscous oil |
| 69 | " | " | H | 4-F | H | " | Na | E | Solid foam |
| 70 | " | " | H | 4-F | H | " | Na | T | Solid foam |
| 71 | cyclohexyl | H | H | 4-F | H | " | CH ₃ | D | Solid foam |
| 72 | cyclohexyl | H | H | 4-F | H | " | Na | E | Amorphous solid |
| 73 | cyclohexyl | H | H | 4-F | H | " | Na | T | Amorphous solid |
| 74 | i-C ₃ H ₇ | 6-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | C ₂ H ₅ | D | Solid foam |
| 75 | " | H | H | 3-CH ₃ | 4-F, 5-CH ₃ | " | C ₂ H ₅ | D | Viscous oil |

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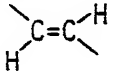
| Cmpd. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ , R _{5a} | X | | Isomer(s) | m.p. |
|--------------|---|--|---|-------------------|-------------------------------------|--|-------------------------------|-----------------|------------------|
| 76 | <u>i</u> -C ₃ H ₇ | H | H | 2-CH ₃ | H |  | Na | E | Amorphous solid |
| 77 | " | H | H | 2-CH ₃ | H | " | Na | T | Amorphous solid |
| 5 78 | " | H | H | 3-CH ₃ | 4-F | " | Na | E | Amorphous solid |
| 79 | " | H | H | 3-CH ₃ | 4-F | " | Na | T | Amorphous solid |
| 80 | " | H | H | 3-CH ₃ | 4-F, 5-CH ₃ | " | Na | E | Amorphous solid |
| 81 | " | 6-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | Na | E | 180°-182° (dec.) |
| 138 | " | 4- <u>i</u> C ₃ H ₇ | 6- <u>i</u> C ₃ H ₇ | 4-F | H | " | C ₂ H ₅ | E | 123.5-125° |
| 10 140 | <u>i</u> -C ₄ H ₉ | H | H | 4-F | H | " | Na | E | 140-160° (dec.) |
| 142 | <u>i</u> -C ₃ H ₇ | H | H | 2-CH ₃ | 4-F | " | Na | E | 155-168° (dec.) |
| 143 | " | H | H | 2-CH ₃ | 4-F | " | CH ₃ | D (mostly E) | |
| 144 | <u>i</u> -C ₄ H ₉ | H | H | 4-F | H | " | CH ₃ | D (mostly E) | |

TABLE II

(Compounds of type IAb: $R_6 = H$; when only one substituent or H appears in column " R_5, R_{5a} " then $R_{5a} = H$)

| Compd. No. | R_1 | R_2 | R_3 | R_4 | R_5, R_{5a} | X | Isomer(s) | m.p. |
|------------|---|--|-------------------|-------------------|-------------------|------------------------------------|--|----------------------|
| 5 82 | CH ₃ | H | H | H | H | | <u>cis</u> | Solid foam |
| 83 | CH ₃ | H | H | H | H | " | <u>trans</u> | 119.5-121° |
| 84 | CH ₃ | 6-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | mixture: ~ 75% <u>trans</u> ~ 25% <u>cis</u> | 145-146° |
| 85 | CH ₃ | H | H | 4-F | H | -CH ₂ CH ₂ - | <u>cis</u> | 164-169°(dec.) |
| 86 | CH ₃ | H | H | 4-F | H | -CH ₂ CH ₂ - | <u>trans</u> | |
| 10 87 | CH ₃ | H | H | 3-CH ₃ | 4-CH ₃ | | <u>cis</u> | Solid foam |
| 88 | CH ₃ | H | H | 3-CH ₃ | 4-CH ₃ | " | <u>trans</u> | Solid foam |
| 89 | i-C ₃ H ₇ | 4-CH ₃ | 6-CH ₃ | 4-F | H | " | ~ 95% <u>cis</u> | 150.5-151° |
| 90 | " | 4-CH ₃ | 6-CH ₃ | 4-F | H | " | <u>trans</u> | 146-147° |
| 91 | CH ₃ | 4-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | <u>cis</u> | Solid foam |
| 15 92 | CH ₃ | 4-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | <u>trans</u> | |
| 93 | CH ₃ | H | H | 3-CH ₃ | 5-CH ₃ | " | <u>cis</u> | Solid foam |
| 94 | CH ₃ | H | H | 3-CH ₃ | 5-CH ₃ | " | <u>trans</u> | Solid foam |
| 95 | CH ₃ | 5-Cl | H | 4-F | H | " | <u>cis</u> | 165.5-166° (dec.) |
| 96 | CH ₃ | 5-Cl | H | 4-F | H | " | <u>trans</u> | 157.5-159° |
| 20 97 | CH ₃ | 5-OCH ₃ | H | 4-F | H | " | <u>cis</u> | Solid foam |
| 98 | CH ₃ | 5-OCH ₃ | H | 4-F | H | " | <u>trans</u> | 102-105° |
| 99 | CH ₃ | 7-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | <u>cis</u> | 127-128.5° |
| 100 | CH ₃ | 7-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | <u>trans</u> | 140.5°-141.5° |
| 101 | CH ₃ | 5-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | mixture: ~ 80% <u>cis</u> ~ 20% <u>trans</u> | 118-119° |
| 25 102 | CH ₃ | " | H | 4-F | H | " | <u>trans</u> | 118-119° |
| 103 | C ₆ H ₅ CH ₂ CH ₂ | H | H | 4-F | H | " | <u>cis</u> | Solid foam |
| 104 | " | H | H | 4-F | H | " | <u>trans</u> | Solid foam |
| 105 | i-C ₃ H ₇ | H | H | 3-CH ₃ | 5-CH ₃ | " | <u>cis</u> | 108-110° |
| 106 | " | H | H | 3-CH ₃ | 5-CH ₃ | " | <u>trans</u> | 145-147° |
| 30 107 | C ₂ H ₅ | H | H | 4-F | H | " | <u>cis</u> | 133.5-135° |
| 108 | " | H | H | 4-F | H | " | <u>trans</u> | 136-137° |
| 109 | i-C ₃ H ₇ | H | H | 3-CH ₃ | 4-F | " | <u>cis</u> | 120-123° |

| Cmpd. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ , R _{5a} | X | Isomer(s) | m.p. |
|--------------|---|--|----------------|-------------------|-------------------------------------|---|--|--------------------|
| 110 | <u>i</u> -C ₃ H ₇ | H | H | 3-CH ₃ | 4-F | | <u>trans</u> | 140.5-141.5° |
| 111 | " | 5-cyclo- hexyl | H | 4-F | H | " | <u>cis</u> | Solid foam |
| 112 | " | " | H | 4-F | H | " | <u>trans</u> | 162-166° |
| 5 113 | cyclohexyl | H | H | 4-F | H | " | <u>cis</u> | Solid foam |
| 114 | " | H | H | 4-F | H | " | <u>trans</u> | Solid foam |
| 115 | <u>i</u> -C ₃ H ₇ | H | H | 2-CH ₃ | H | " | <u>cis</u> | Solid foam |
| 116 | " | H | H | 2-CH ₃ | H | " | <u>trans</u> | Solid foam |
| 117 | " | H | H | 3-CH ₃ | 4-F, 5-CH ₃ | " | mixture: ~ 88% <u>cis</u> ~ 12% <u>trans</u> | 107-113° |
| 10 118 | " | H | H | 3-CH ₃ | 4-F, 5-CH ₃ | " | <u>trans</u> | 166.5-167.5° |
| 119 | " | 6-OCH ₂ C ₆ H ₅ | H | 4-F | H | " | <u>trans</u> | 152-153° (dec.) |
| 139 | <u>i</u> -C ₄ H ₉ | H | H | 4-F | H | " | <u>trans</u> | 51-55°(dec.) |
| 141 | <u>i</u> -C ₃ H ₇ | H | H | 2-CH ₃ | 4-F | " | <u>trans</u> | 64-69° |

TABLE III

(Compounds of type IBa; when only one substituent or H appears in column "R₅, R_{5a}" then R_{5a} = H)

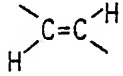
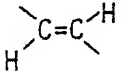
| Cmpd. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ , R _{5a} | X | R ₆ | R ₇ | Isomer(s) | m.p. |
|-----------|---------------------------------|--------------------|----------------|-------------------|----------------------------------|--|-----------------|-------------------------------|-----------|-------------|
| 120 | CH ₃ | H | H | 4-F | H |  | H | C ₂ H ₅ | D | |
| 121 | CH ₃ | H | H | 4-F | H | " | H | K | D | |
| 122 | CH ₃ | H | H | 4-F | H | " | H | H | D | |
| 123 | C ₂ H ₅ | 5-OCH ₃ | H | 3-CH ₃ | H | -CH ₂ CH ₂ - | CH ₃ | CH ₃ | D | |
| 124 | C ₂ H ₅ | 5-OCH ₃ | H | 3-CH ₃ | H | -CH ₂ CH ₂ - | CH ₃ | K | D | |
| 125 | C ₂ H ₅ | 5-OCH ₃ | H | 3-CH ₃ | H | -CH ₂ CH ₂ - | CH ₃ | H | D | |
| 126 | i-C ₃ H ₇ | H | H | 4-F | H |  | H | C ₂ H ₅ | D | |
| 127 | " | H | H | 4-F | H | " | H | K | D | |
| 128 | " | H | H | 4-F | H | " | H | H | D | |
| 129 | CH ₃ | H | H | H | H | " | H | C ₂ H ₅ | D | Viscous oil |

TABLE IV

(Compounds of type IBb); when only one substituent or H appears in column "R₅, R_{5a}" then R_{5a} = H)

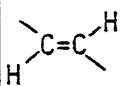
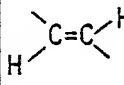
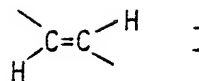
| Cmpd. No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ , R _{5a} | X | R ₆ | Isomer(s) | m.p. |
|-----------|---|--------------------|----------------|-------------------|-------------------------------------|--|-----------------|--------------|-------------|
| 5 130 | CH ₃ | H | H | 4-F | H |  | H | <u>cis</u> | |
| 131 | CH ₃ | H | H | 4-F | H | " | H | <u>trans</u> | |
| 132 | C ₂ H ₅ | 5-OCH ₃ | H | 3-CH ₃ | H | -CH ₂ CH ₂ - | CH ₃ | <u>cis</u> | |
| 133 | C ₂ H ₅ | 5-OCH ₃ | H | 3-CH ₃ | H | -CH ₂ CH ₂ - | CH ₃ | <u>trans</u> | |
| 134 | <u>i</u> -C ₃ H ₇ | H | H | 4-F | H |  | H | <u>cis</u> | |
| 10 135 | " | H | H | 4-F | H | " | H | <u>trans</u> | |
| 136 | CH ₃ | H | H | H | H | " | H | <u>cis</u> | Solid foam |
| 137 | CH ₃ | H | H | H | H | " | H | <u>trans</u> | Viscous oil |

TABLE V

[Compounds of type IV (sub-type XX) wherein X is



| Cmpd. No. | R | R ₀ | R ₂ | R ₃ | m.p. |
|-----------|---|---|--|-----------------------------------|-----------------------|
| IVe | 3,4-di-CH ₃ -C ₆ H ₃ - | CH ₃ | H | H | 97-99° |
| IVf | 4-F-C ₆ H ₄ - | C ₆ H ₅ CH ₂ CH ₂ - | H | H | 86-88° |
| IVg | 4-F-C ₆ H ₄ - | i-C ₃ H ₇ | 5-cyclohexyl | H | 162-167° |
| IVh | 2-CH ₃ -C ₆ H ₄ - | i-C ₃ H ₇ | H | H | 190-193° |
| IVi | 3,5-di-CH ₃ -C ₆ H ₅ - | CH ₃ | H | H | 117-118.5° |
| IVj | 4-F-C ₆ H ₄ - | CH ₃ | 5-OCH ₃ | H | 137-138.5° |
| IVk | 4-F-C ₆ H ₄ - | CH ₃ | 6-OCH ₂ C ₆ H ₅ | H | 128.5-131° |
| IVl | 4-F-C ₆ H ₄ - | CH ₃ | 4-OCH ₂ C ₆ H ₅ | H | 162.5-164° |
| IVm | 4-F-C ₆ H ₄ - | CH ₃ | 5-Cl | H | 169.5-170.5° |
| IVn | C ₆ H ₅ - | CH ₃ | H | H | 141.5-142.5° |
| IVo | 4-F-C ₆ H ₄ - | CH ₃ | 7-OCH ₂ C ₆ H ₅ | H | 140-141° |
| IVp | 4-F-C ₆ H ₄ | CH ₃ | 5-OCH ₂ C ₆ H ₅ | H | 124.5-125° |
| IVq | 3-CF ₃ C ₆ H ₄ - | CH ₃ | H | H | 124-124.5° |
| IVr | 4-F-C ₆ H ₄ - | C ₂ H ₅ | H | H | 103-105° |
| IVs | 4-F-C ₆ H ₄ - | i-C ₃ H ₇ | 4-CH ₃ | 6-CH ₃ | 189-190° |
| IVt | C ₆ H ₅ - | i-C ₃ H ₇ | H | H | 111-112° |
| IVu | 3,5-di-CH ₃ -4-F-C ₆ H ₂ - | i-C ₃ H ₇ | H | H | 114.5°-115° |
| IVv | 4-F-C ₆ H ₄ - | i-C ₃ H ₇ | 6-OCH ₂ C ₆ H ₅ | H | 118.5-120° |
| IVw | 4-F-C ₆ H ₄ - | i-C ₃ H ₇ | 4-i-C ₃ H ₇ | 6-i-C ₃ H ₇ | 162-163° |
| IVx | CH ₃ | C ₆ H ₅ - | H | H | crude amorphous solid |

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TABLE VI
(Compounds of type XXIV)

| Compound No. | R | R ₀ | R ₂ | R ₃ | Y ^θ | m.p. |
|--------------|-------------------------------------|---------------------------------|----------------|----------------|-----------------|----------|
| XXIVb | 4-F-C ₆ H ₄ - | i-C ₃ H ₇ | H | H | Cl ^θ | 236-239° |



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Each of the compounds of Tables I and III denoted by a D in the Isomer(s) column is a mixture of four stereoisomers which may be separated. The four optically pure enantiomers that may be obtained may be designated as the 3R,5R, 3S,5S, 3R,5S and 3S,5R isomers. Except in the case of compounds 123-125 preferred are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, viz., the 3R,5R-3S,5S (threo) racemate and the 3R,5S-3S,5R (erythro) racemate, of which the latter is preferred. The preferred isomers of compounds 123-125 are the 3R,5R and 3R,5S isomers and the racemate of which is a constituent, viz., the 3R,5R-3S,5S (erythro) racemate and the 3R,5S-3S,5R (threo) racemate, of which the former is preferred. Each of the compounds of Tables I and III denoted by an E in the Isomer(s) column is the erythro racemate which may be resolved to obtain the 3R,5S and 3S,5R enantiomers by, for example, (i) lactonization, (ii) conversion to a mixture of two diastereoisomeric silyloxy compounds, (iii) chromatographic separation of the diastereoisomeric silyloxy compounds, (iv) cleavage of the silyl group and (v) hydrolysis of the obtained optically pure lactone, as set forth in more detail above. Each of the compounds of Tables I and III denoted by a T in the Isomer(s) column is the threo racemate which may be resolved by, for example, the same procedure to obtain the 3R,5R and 3S,5S enantiomers.

Each of the compounds of Tables II and IV denoted by cis in the Isomer(s) column is the cis racemate and each of the compounds of these tables denoted by trans in the isomer column is the trans racemate, cis and trans referring to the relative positions of the hydrogen atoms in the 4- and 6-positions of the lactone ring. The cis racemates of compounds 85 and 132 may be resolved to obtain the 4R,6S and 4S,6R enantiomers and each of the other cis racemates of Tables II and IV may be resolved to obtain the 4R,6R and 4S,6S enantiomers, of which the 4R,6S and 4R,6R enantiomers are preferred. The trans racemates of Compounds



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86 und 133 may be resolved to obtain the 4R,6R and 4S,6S enantiomers, and each of the other trans racemates of Tables II and IV may be resolved to obtain the 4R,6S and 4S,6R enantiomers, of which the 4R,6R and 4R,6S enantiomers are preferred. The cis and trans racemates may be resolved by Steps (ii)-(iv) of the procedure outlined in the preceding paragraph.

The following data were obtained for the preceding compounds. Unless otherwise stated the data are NMR spectra measured at 200 MHz. Shifts are in ppm. relative to tetramethylsilane.

Abbreviations:

s = singlet
d = doublet
dd = doublet of a doublet
t = triplet
q = quartet
Q = quintet
m = multiplet
br = broad
bs = broad singlet
dq = doublet of a quartet
dt = doublet of a triplet



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| Cmpd. no. | |
|-----------|---|
| 1 | CDCl ₃ : 1.5-1.9(m,2H); 2.4-2.6 (m,2H); 2.8-3.4(br.,2H :D ₂ O exch); 3.7(s,3H); 3.8(s,3H); 4.26(m,1H); 4.55(m,1H); 5.85-6.1(m,1H); 6.7(2d,1H); 7.05-7.55 (m,8H). |
| 5 | 4 CDCl ₃ : 1.6-3.0(m,5H); 3.82(2s,3H); 4.39(m,1H); 4.78(m, ¹ / ₂ H: <u>cis</u> /C ₆ -H); 5.3(m, ¹ / ₂ H: <u>trans</u> /C ₆ -H); 5.82-6.0(m,1H); 6.69-6.81 (2d,1H); 7.05-7.6(m,8H). |
| | 11 CDCl ₃ : 1.68(d,6H); 1.75-2.05(m,3H); 2.55-2.82(m,2H); 4.38(m,1H); 4.82(q,1H); 5.25(m,1H); 5.72(q,1H); 6.75(d,1H); 7.05-7.6(m,8H); |
| 10 | 13 CDCl ₃ /CD ₃ OD : 1.55(m,1H); 1.6(d,6H), 2.2-2.45 (m,3H); 4.08(m,1H); 4.42 (m,1H); 4.9(q,1H); 5.75(dd,1H); 6.68(d,1H); 7.0-7.2(m,4H); 7.48-7.58(m,4H). |
| | 16 D ₂ O : 1.05(d,6H); 1.28(m,2H); 2.18(d,2H); 3.95(m,1H); 4.2(m,1H); 4.5(m,1H); 5.4(dd,1H); 6.4(d,1H); 6.5-7.2(m,8H). |
| 15 | 18 CDCl ₃ : 1.71(m,1H); 2.05(m,1H); 2.31(m,1H); 2.52(dd;J ₁ =17.5Hz; J ₂ =8Hz; 1H); 2.95(dd,J ₁ =17.5Hz; J ₂ =5.5Hz; 1H); 3.85 (s,3H); 4.31(m,1H); 4.81(m,1H); 5.97(dd,J ₁ =16Hz; J ₂ =6Hz; 1H); 6.77 (d,J=16Hz; 1H); 7.09-7.72(m,8H). |
| 20 | 19 CDCl ₃ : 0.75(m,1H); 1.14(m,1H); 1.49(m,1H); 2.48(m,2H); 3.76(s,3H); 4.1(bs,1H); 5.1(m,1H); 5.89(dd,J ₁ =10.5Hz; J ₂ =10Hz; 1H); 6.7(d,J=10.5Hz, 1H); 7.09-7.73(m,8H). |
| | 22 CDCl ₃ : 1.29(t,3H); 1.51-1.88(m,2H); 2.48(d,2H); 3.83(s,3H); 4.08-4.37(m,3H); 4.54(m,1H); 5.96(m,1H); 6.76(m,1H); 7-7.68(m,9H). |
| 25 | 25 D ₂ O : 1.38-1.73(m,2H); 2.12-2.26(m,2H); 3.60(s,3H); 3.85(m,1H); 4.25 (m,1H), 5.75 (dd,1H); 6.52(d,1H); 6.96-7.50(m,9H). |
| | 26 D ₂ O : 1.41(t,2H); 2.20(d,2H); 3.36(s,3H); 4.0(m,1H); 4.2(m,1H); 5.66(dd,1H); 6.38(d,1H); 6.78-7.39(m,9H). |
| 30 | 27 CDCl ₃ : 1.26(t,3H); 1.68(m,2H); 2.45(d,2H); 3.69(s,3H); 4.17(q,2H); 4.25(m,1H); 4.50(m,1H); 5.10(s,2H); 5.88(m,1H); 6.65(m,1H); 7.09(t,2H); 7.44(m,9H); 7.85(d,2H). |



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| Cmpd. no. | | |
|-----------|----|---|
| | 29 | $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.49-1.80(m,2H); 2.17-2.44(m,2H); 3.75(s,3H); 4.09(m,1H); 4.42(m,1H); 5.13(s,2H); 5.90(dd,1H); 6.63(d,1H); 6.77-6.92(m,2H); 7.09(t,2H); 7.27-7.54(m,8H). |
| 5 | 34 | CDCl_3 : 1.28(t,3H); 1.6-1.8(m,2H); 2.3(s,6H); 2.48(m,2H); 3.82(s,3H); 4.18(q,2H); 4.3(m,1H); 4.55(m,1H); 6.0(m,1H); 6.75(2d,1H); 7.05-7.65(m,7H). |
| | 38 | CDCl_3 : 1.45-1.82(m,2H); 1.68(d,6H); 2.48(m,2H); 3.22(d,1H, exchangeable); 3.59(m,1H, exchangeable); 3.75(s,3H); 4.2(m,1H); 4.5 (m,1H); 4.86(q,1H); 5.75(m,1H); 6.72(2d,1H); 7.05-7.55(m,8H). |
| 10 | 41 | CDCl_3 : 1.28(t,3H); 1.61(m,2H); 2.42(m,2H); 3.80(s,3H); 4.13(q,2H); 4.45(bs,1H); 4.96(s,2H); 5.72(m,1H); 6.56(m,1H); 6.90(m,5H); 7.24(m,7H). |
| | 44 | CDCl_3 : 1.5-1.85(m,2H); 1.27(t,3H); 2.35(s,6H); 2.43-2.5(m,2H); 3.79(s,3H); 4.28(m,1H), 4.53(m,1H); 5.97(m,1H); 6.73(m,1H); 6.94-7.35(m,5H); 7.62(d,2H). |
| 15 | 47 | D_2O : 1.86(s,6H); 3.18(s,3H). |
| | 48 | D_2O : 2.10(s,6H); 3.48(s,3H). |
| | 52 | CDCl_3 : 1.28(t,3H); 1.70(m,2H); 2.46(d,2H); 3.78(s,3H); 3.81(s,3H); 4.19(q,2H); 4.24(bs,1H); 5.89(m,1H); 6.68(m,1H); 6.94(m,2H); 7.17(m,3H); 7.41(m,2H). |
| 20 | 55 | $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.42-1.73(m,2H); 2.12-2.42(m,2H); 4.07(s,3H); 4.40(m,1H); 5.2(s,2H); 5.83(dd,1H); 6.53-6.75(m,2H); 6.89-7.14 (m,3H); 7.27-7.50(m,8H). |
| 25 | 56 | $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.41-1.67(m,2H); 2.20-2.33(m,2H); 4.03(s,3H); 3.98-4.18(m,1H); 4.33(m,1H); 5.15(s,2H); 5.83(dd,1H); 6.59-6.73 (m,2H); 6.85-7.13(m,4H); 7.24-7.50(m,6H). |
| | 57 | CDCl_3 : 1.28(t,3H); 1.51-1.87(m,2H); 2.37-2.62(m,2H); 3.75(s,3H); 4.08-4.33(m,3H); 4.52(m,1H); 5.02(s,2H); 5.90(m,1H); 6.57-6.73 (m,1H); 6.92-7.47(m,12H). |
| 30 | | |



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Cmpd.no.

- 58 CDCl_3 : 1.4-1.8(m,2H); 2.45(m,2H); 2.84(m,1H, exchangeable); 3.1(t,2H); 3.45(m,1H, exchangeable); 3.72(s,3H); 4.2(m,1H); 4.42(t,2H); 5.72(m,1H); 6.4(d,1H); 7-7.55(m,13H).
- 5 59 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.48(m,1H); 2.25(m,3H); 2.92(m,2H); 4.2(m,4H); 5.75(dd,1H); 6.45(d,1H); 6.9-7.5(m,13H).
- 60 CDCl_3 : 1.27(t,3H); 1.40(t,3H); ~ 1.40-1.85(m,2H); 2.33-2.61(m,2H); 4.03-4.35(m,5H); 4.53(m,1H); 5.89(m,1H); 6.60-6.78(m,1H); 7.0-7.57(m,8H).
- 10 61 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.16-1.74(m,5H); 2.12-2.47(m,2H); 4.12(m,1H); 4.27(q,2H); 4.41(m,1H); 5.88(dd,1H); 6.65(d,1H); 7.0-7.56(m,8H);
- 62 CDCl_3 : 1.40(t,3H); 1.50-1.68(m,2H); 2.19-2.38(m,2H); 4.12(m,1H); 4.28(q,2H); 4.47(m,1H); 5.90(dd,1H); 6.67(d,1H); 7.0-7.54(m,8H).
- 15 64 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.15-1.6(m,2H); 1.65(d,6H); 2.01(s,3H); 2.1-2.4(m,2H); 2.45(s,3H); 3.92(m,1H); 4.29(m,1H); 4.84(m,1H); 5.58(dd,1H); 6.52(d,1H); 6.60(s,1H); 6.96-7.37(m,5H).
- 65 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.3-1.65(m,2H); 1.67(d,6H); 2.01(s,3H); 2.15-2.35(m,2H); 2.43(s,3H); 3.98(m,1H); 4.34(m,1H); 4.85(m,1H); 5.54(dd,1H); 6.53(d,1H); 6.61(s,1H); 6.95-7.38(m,5H).
- 20 66 CDCl_3 : 1.55(m,2H); 1.65(d,6H); 2.33(s,6H); 2.45(m,2H); 3.72(s,1H); 4.20(m,1H); 4.50(m,1H); 4.85(Q,1H); 5.75(dd,1H); 6.7(dd,1H); 6.9-7.6(m,7H).
- 68 CDCl_3 : 1.1-1.6(m,7H); 1.62(d,6H); 1.62-1.94(m,5H); 2.4-2.62(m,3H); 3.0-3.6(br,2H); 3.75(s,3H); 4.15(m,1H); 4.5(m,1H); 4.82(Q,1H); 5.6-5.8(m,1H); 6.7(d,1H); 7.05-7.45(m,7H).
- 25 69 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.15-1.6(m,7H); 1.65(d,6H); 1.7-1.95(m,5H); 2.15-2.44(m,2H); 2.48-2.62(m,1H); 4.04(m,1H); 4.38(m,1H); 4.85(Q,1H); 5.7(dd,1H); 6.65(d,1H); 7.0-7.15(m,3H); 7.3-7.5(m,4H).

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| Cmpd.no. | | |
|----------|----|---|
| | 70 | $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.15-1.6(m,8H); 1.64(d,6H); 1.7-2(m,4H); 2.3(m,2H); 2.55(m,1H); 4.1(m,1H); 4.46(m,1H); 4.85(Q,1H); 5.72(dd,1H); 6.65(d,1H); 7.1(m,3H); 7.4(m,4H); |
| 5 | 71 | CDCl_3 : 1.3-2.05(m,11H); 2.2-2.5(m,3H); 3.1-3.6(br,2H); 3.72(s,3H); 4.05-4.6(m,3H); 5.7(m,1H); 6.7(m,1H); 7.0-7.6(m,8H). |
| | 72 | $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.5(m,4H); 1.95(m,6H); 2.3(m,4H); 4.1(m,1H); 5.72(dd,1H); 6.7(d,1H); 7.1(m,4H); 7.5(m,4H). |
| 10 | 73 | $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.2-1.62(m,5H); 1.74-2.05(m,5H); 2.18-2.46(m,4H); 4.14(m,1H); 4.46(m,1H); 5.75(dd,1H); 6.68(d,1H); 7.0-7.2(m,4H); 7.3-7.6(m,4H). |
| | 74 | CDCl_3 : 1.3(t,3H); 1.4-1.82(m,2H); 1.60(d,6H); 2.38-2.58(m,2H); 4.20(q,2H); 4.50(m,1H); 4.78(m,1H); 5.13(s,2H); 5.55-5.78(m,1H); 6.57-6.74(m,2H); 6.83(d,1H); 6.98-7.14(m,3H); 7.24-7.55(m,8H). |
| 15 | 75 | CDCl_3 : 1.28(t,3H); 1.41-1.81(m,2H); 1.64(d,6H); 2.25-3.58(m,2H); 2.27(s,6H); 4.18(q,2H); 4.52(m,1H); 4.83(m,1H); 5.62-5.84(m,1H); 6.61-6.76(m,1H); 6.98-7.23(m,4H); 7.43-7.56(m,2H). |
| | 76 | $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.3(m,1H); 1.5(m,1H); 1.7(d,6H); 2.1(d,3H); 2.22(m,2H); 3.9(m,1H); 4.3(m,1H); 4.9(Q,1H); 5.55(dt,1H); 6.65(d,1H); 6.95-7.55(m,8H). |
| 20 | 77 | $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.3-1.6(m,2H); 1.7(d,6H); 2.1(d,3H); 2.24(m,2H); 3.96(m,1H); 4.35(m,1H); 4.9(Q,1H); 5.58(dd,1H); 6.68(d,1H); 7.0-7.5(m,8H). |
| | 78 | $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.45-1.81(m,2H); 1.57(d,6H); 2.15-2.46(m,2H); 2.30(s,3H); 4.88(m,1H); 5.73(dd,1H); 6.68(d,1H); 6.95-7.70(m,7H). |
| 25 | 79 | $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.42-1.62(m,2H); 1.68(d,6H); 2.17-2.35(m,5H); 4.1(m,1H); 4.45(m,1H); 4.90(m,1H); 5.78(dd,1H); 6.70(d,1H); 6.95-7.58(m,7H). |

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Cmpd. no.

- 80 $\text{CDCl}_3/\text{CD}_3\text{OD}$: 1.4—1.65(m,2H); 1.67(d,6H); 2.28(d,6H);
2.12-2.45(m,2H); 4.43(m,1H); 4.88(m,1H); 5.74(dd,1H);
6.67(d,1H); 6.98-7.22(m,4H); 7.53(d,2H).
- 5 82 CDCl_3 : 1.61-3.0(m,5H); 3.87(s,3H); 4.29(m,1H); 4.79(m,1H);
5.98(dd,1H); 6.80(d,1H); 7.13(t,1H); 7.24-7.5(m,7H); 7.62(d,1H).
- 87 CDCl_3 : 1.58(s,1H); 1.82(m,1H); 1.9(m,1H); 2.35(s,6H); 2.5(q,1H);
2.95(q,1H); 3.85(s,3H); 4.3(m,1H); 4.8(m,1H); 6.0(q,1H);
6.8(d,1H); 7.05-7.65(m,7H).
- 10 88 CDCl_3 : 1.6(s,1H); 1.8-2.1(m,2H); 2.35(s,6H); 2.7(m,2H);
3.85(s,3H); 4.38(m,1H); 5.3(m,1H); 6.0(q,1H); 6.8(d,1H);
7.05-7.65(m,7H).
- 93 CDCl_3 : 1.65-2.1(m,2H); 2.52-2.8(m,2H); 2.38(s,6H); 3.85(s,3H);
4.80(m,1H); 5.98(m,1H); 6.79(d,1H); 6.93-7.38(m,6H); 7.62(d,1H).
- 94 CDCl_3 : 1.3-3.0(m,4H); 2.38(s,6H); 3.82(s,3H); 5.30(m,1H);
5.95(dd,1H); 6.78(d,1H); 6.93-7.40(m,6H); 7.62(d,1H).
- 97 CDCl_3 : 1.61-3.02(m,5H); 3.83(s,3H); 4.31(m,1H); 4.78(m,1H);
5.90(dd,1H); 6.73(d,1H); 6.94(m,2H); 7.1-7.38(m,3H); 7.40(m,2H).
- 103 CDCl_3 : 1.55(m,1H); 2.18(m,1H); 2.28(s,1H); 2.46(q,1H); 2.9(q,1H);
20 3.06(t,2H); 4.22(m,1H); 4.4(t,2H); 4.6(m,1H); 5.68(dd,1H);
6.4(d,1H); 7.05-7.55(m,13H).
- 104 CDCl_3 : 1.55-1.95(m,2H); 2.42(s,1H, exchangeable); 2.65(m,2H);
3.05(t,2H); 4.3(m,1H); 4.4(t,2H); 5.15(m,1H); 5.68(dd,1H);
6.4(d,1H); 7.05-7.55(m,13H).
- 25 111 CDCl_3 : 1.1-1.35(m,5H); 1.65(d,6H); 1.65-2.0(m,5H); 2.05-2.3
(m,2H); 2.4-2.6(m,2H); 2.92(dd,1H); 4.25(m,1H); 4.78(m,2H);
5.65(dd,1H); 6.72(d,1H); 7.02-7.48(m,7H).
- 113 CDCl_3 : 1.2-2.55(m,14H); 2.92(q,1H); 4.3(m,2H); 4.78(m,1H);
5.68(dd,1H); 6.75(d,1H); 7.0-7.6(m,8H).
- 30 114 CDCl_3 : 1.2-2.05(m,10H); 2.2-2.45(m,2H); 2.7(m,2H); 4.3(m,2H);
5.25(m,1H); 5.65(dd,1H); 6.72(d,1H); 7.0-7.6(m,8H).



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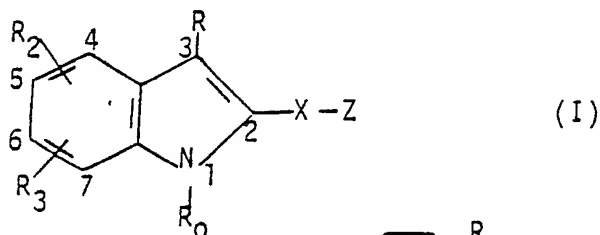
- Cmpd. no.
- 115 CDCl₃ : 1.3-1.52(m,2H); 1.7(d,6H); 1.8(m,1H, exchangeable);
2.1(d,3H); 2.48(dd,1H); 2.9(dd,1H); 4.2(m,1H); 4.68(m,1H);
4.82(Q,1H); 5.5(m,1H); 6.7(d,1H); 7.0-7.5(m,8H).
- 5 116 CDCl₃ : 1.68-1.9(m,9H); 2.1(s,3H); 2.64(dq,2H); 4.18(m,1H);
4.85(Q,1H); 5.16(m,1H); 5.45(dt,1H); 6.7(d,1H); 7.0-7.5(m,8H).
- 129 CDCl₃ : 1.28(t,3H); 1.50-1.83(m,2H); 2.45(d,2H); 4.11-4.32(m,3H);
4.47(m,1H); 5.75(m,1H); 6.52(m,1H); 7.02-7.62(m,9H).
- 10 136 CDCl₃ : 1.55-2.97(m,5H); 2.48(s,3H); 4.24(m,1H); 4.70(s,1H);
5.72(dd,1H); 6.57(d,1H); 7.04-7.63(m,9H).
- 137 (CDCl₃) : 1.18-2.08(m,3H); 2.5(s,3H); 2.53-2.82(m,2H); 4.38
(m,1H); 5.21(m,1H); 5.72(m,1H); 6.58(d,1H); 7.07-7.65(m,9H).
- 143 CDCl₃ : 1.42(m,2H); 1.66(d,6H); 2.09(d,3H); 2.42(d,2H);
3.72(s,3H); 4.05(m,1H); 4.39(m,1H); 4.84(Q,1H); 5.48(dd,1H);
15 6.67(d,1H); 6.90-7.56(m,7H).
- 144 CDCl₃ : 0.95(d,6H); 1.57(m,2H); 2.25(Q,1H); 2.48(d,2H); 3.74(s,3H);
4.01(d,2H); 4.22(m,1H); 4.48(m,1H); 5.78(dd,1H); 6.67(d,1H);
7.04-7.51(m,8H).



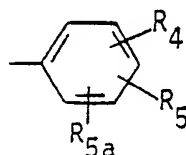
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Claims:

1. Compounds of formula I



wherein one of R and R₀ is



and the other is

primary or secondary C₁₋₆alkyl, C₃₋₆cycloalkyl or phenyl-(CH₂)_m-,

wherein R₄ is hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R₅ is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_{5a} is hydrogen, C₁₋₂alkyl, C₁₋₂alkoxy, fluoro or chloro, and

m is 1, 2 or 3,

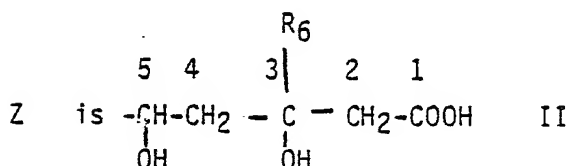
with the provisos that both R₅ and R_{5a} must be hydrogen when R₄ is hydrogen, R_{5a} must be hydrogen when R₅ is hydrogen, not more than one of R₄ and R₅ is trifluoromethyl, not more than one of R₄ and R₅ is phenoxy and not more than one of R₄ and R₅ is benzyloxy,

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R₂ is hydrogen, C₁₋₄alkyl, C₃₋₆cyclo-alkyl, C₁₋₄alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

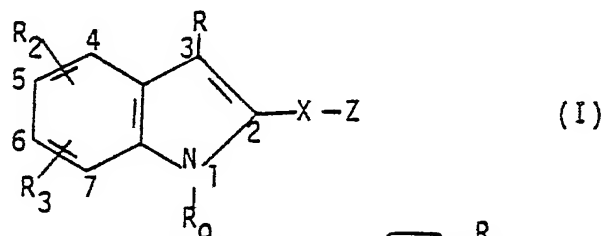
R₃ is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R₃ must be hydrogen when R₂ is hydrogen, not more than one of R₂ and R₃ is trifluoromethyl, not more than one of R₂ and R₃ is phenoxy, and not more than one of R₂ and R₃ is benzyloxy,

X is -(CH₂)_n- or -CH=CH- (n=0, 1, 2 or 3),

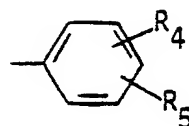


wherein R₆ is hydrogen or C₁₋₃alkyl in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a δ -lactone thereof or in salt form.

2. A compound according to Claim 1, wherein



wherein one of R and R₀ is



and the other is

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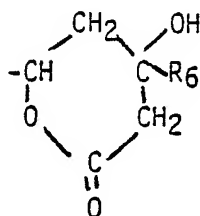
C₁-3alkyl, n-butyl or i-butyl,
 wherein R₄ is hydrogen, C₁-3alkyl, n-butyl,
 i-butyl, C₁-3alkoxy, n-butoxy,
 i-butoxy, trifluoromethyl, fluoro,
 chloro, phenoxy or benzyloxy, and
 R₅ is hydrogen, C₁-3alkyl, C₁-3alkoxy,
 trifluoromethyl, fluoro, chloro,
 phenoxy, or benzyloxy,
 with the provisos that not more
 than one of R₄ and R₅ is trifluoro-
 methyl, not more than one of R₄ and
 R₅ is phenoxy, and not more than
 one of R₄ and R₅ is benzyloxy,

R₂ is hydrogen, C₁-3alkyl, n-butyl, i-butyl,
 C₁-3alkoxy, n-butoxy, i-butoxy, trifluoro-
 methyl, fluoro, chloro, phenoxy or benzyloxy,
 R₃ is hydrogen, C₁-3alkyl, C₁-3alkoxy, trifluoro-
 methyl, fluoro, chloro, phenoxy or benzyloxy,
 with the provisos that not more than one of R₂
 and R₃ is trifluoromethyl, not more than one
 of R₂ and R₃ is phenoxy, and not more than one
 of R₂ and R₃ is benzyloxy,

X is $-(CH_2)_n-$ or $\begin{array}{c} \text{H} \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{H} \end{array}$,

wherein n is 0, 1, 2 or 3, and

Z is $\begin{array}{c} \text{R}_6 \\ | \\ -\text{CH}-\text{CH}_2-\text{C}-\text{CH}_2-\text{COOR}_7' \\ | \quad | \\ \text{OH} \quad \text{OH} \end{array}$ or



-72-

wherein R_6 is hydrogen or C_{1-3} alkyl, and
 R_7' is hydrogen, C_{1-3} alkyl, n-butyl,
i-butyl, t-butyl, benzyl or M,
wherein M is a pharmaceutically
acceptable cation.

3. A compound according to Claim 1, wherein R is p-fluoro-phenyl, R_0 is isopropyl, R_2 and R_3 are hydrogen, X is (E)CH=CH, R_6 is hydrogen in erythro form and 3R,5S configuration and in the form of its sodium salt.

4. A pharmaceutical composition comprising a compound according to Claim 1 in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form, together with a pharmaceutically acceptable diluent or carrier.

5. The use of a compound according to Claim 1 in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form in inhibiting cholesterol biosynthesis or treating atherosclerosis.

6. A compound according to Claim 1 in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form for use as a pharmaceutical.

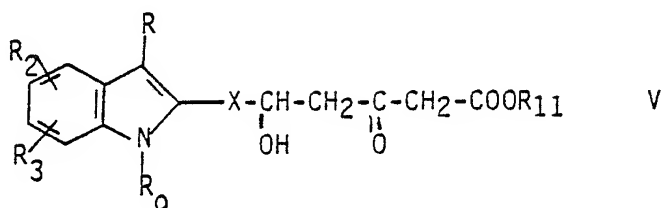
7. A compound according to Claim 1 in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form for use in inhibiting cholesterol biosynthesis or treating atherosclerosis.



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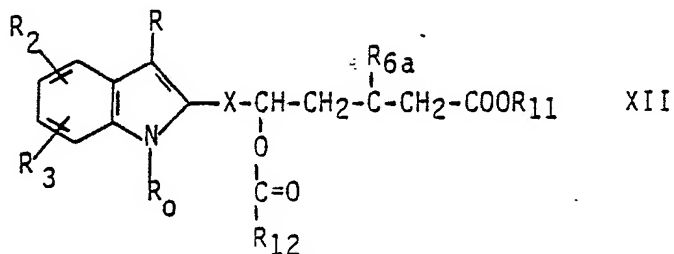
8. A process for preparing a compound according to Claim 1 which comprises

a) when R_6 is hydrogen, reducing a compound of formula V



wherein R_{11} is a radical forming a physiologically-hydrolyzable and -acceptable ester and X, R, R_0 , R_2 and R_3 are as defined above,

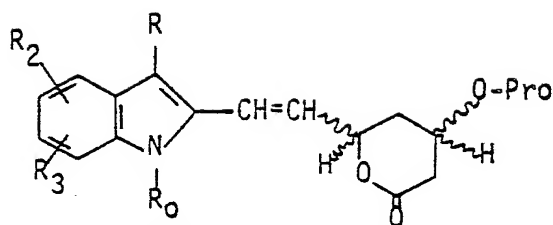
b) when $R_6 = C_{1-3}$ alkyl, hydrolysing a compound of formula XII



wherein R_{6a} is C_{1-3} alkyl, R_{12} is an ester forming group and X, R, R_0 , R_3 and R_{11} are as defined above,

c) when X is $-CH=CH-$ deprotecting a compound of formula XXVIII

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XXVIII

wherein Pro is a protecting group and R, R₀, R₂ and R₃ are as defined above,

- d) hydrolysing a compound of formula I in the form of a physiologically-hydrolysable ester or a lactone or
 5 e) esterifying or lactonising a compound of formula I in free acid form,

and when a free carboxyl group is present, recovering the compound obtained in free form or in the form of a salt.

9. A compound of formula V, X, XI, XII, XX, XXA, XXIV, XXVI-XXVIII and XXIXB-XXIXD as hereinbefore defined.
 10

10. A compound according to Claim 1 or 9 or a process according to Claim 8 substantially as hereinbefore described with reference to Examples 1 to 10 and Tables I to VI.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 83/00308

| I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ³ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ³ : C 07 D 209/18; C 07 D 405/04; A 61 K 31/405 | | | | | | | | |
|---|--|-------------------------------------|--|--|--|---|--|---|
| II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Minimum Documentation Searched ⁴</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border: 1px solid black; padding: 5px;">Classification System</th> <th style="border: 1px solid black; padding: 5px;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; padding: 10px; vertical-align: top;">IPC³</td> <td style="border: 1px solid black; padding: 10px; vertical-align: top;">C 07 D 209/00; C 07 D 405/00</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵</div> | | | Classification System | Classification Symbols | IPC ³ | C 07 D 209/00; C 07 D 405/00 | | |
| Classification System | Classification Symbols | | | | | | | |
| IPC ³ | C 07 D 209/00; C 07 D 405/00 | | | | | | | |
| III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border: 1px solid black; padding: 5px;">Category [*]</th> <th style="width: 70%; border: 1px solid black; padding: 5px;">Citation of Document, ¹⁵ with indication, where appropriate, of the relevant passages ¹⁷</th> <th style="width: 20%; border: 1px solid black; padding: 5px;">Relevant to Claim No. ¹⁸</th> </tr> <tr> <td style="border: 1px solid black; padding: 10px; vertical-align: top; text-align: center;">A</td> <td style="border: 1px solid black; padding: 10px; vertical-align: top;"> Tetrahedron Letters, vol. 23, no. 42, 1982, Pergamon Press Ltd. (GB) Y.L Yang et al.: "Mevinic acids and analogues: preparation of a key chiral intermediate", pages 4305-4308, see the whole document cited in the application <div style="text-align: center; margin-top: 20px;">-----</div> </td> <td style="border: 1px solid black; padding: 10px; vertical-align: top; text-align: center;">1</td> </tr> </table> | | | Category [*] | Citation of Document, ¹⁵ with indication, where appropriate, of the relevant passages ¹⁷ | Relevant to Claim No. ¹⁸ | A | Tetrahedron Letters, vol. 23, no. 42, 1982, Pergamon Press Ltd. (GB) Y.L Yang et al.: "Mevinic acids and analogues: preparation of a key chiral intermediate", pages 4305-4308, see the whole document cited in the application <div style="text-align: center; margin-top: 20px;">-----</div> | 1 |
| Category [*] | Citation of Document, ¹⁵ with indication, where appropriate, of the relevant passages ¹⁷ | Relevant to Claim No. ¹⁸ | | | | | | |
| A | Tetrahedron Letters, vol. 23, no. 42, 1982, Pergamon Press Ltd. (GB) Y.L Yang et al.: "Mevinic acids and analogues: preparation of a key chiral intermediate", pages 4305-4308, see the whole document cited in the application <div style="text-align: center; margin-top: 20px;">-----</div> | 1 | | | | | | |
| <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹⁶</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div> | | | | | | | | |
| IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of the Actual Completion of the International Search ¹ 7th March 1984 </td> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of Mailing of this International Search Report ³ 18 AVR. 1984 </td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;"> International Searching Authority ¹ EUROPEAN PATENT OFFICE </td> <td style="border: 1px solid black; padding: 5px;"> Signature of Authorized Officer ²⁰ <div style="text-align: right;"> G.L.M. Krundenberg </div> </td> </tr> </table> | | | Date of the Actual Completion of the International Search ¹ 7th March 1984 | Date of Mailing of this International Search Report ³ 18 AVR. 1984 | International Searching Authority ¹ EUROPEAN PATENT OFFICE | Signature of Authorized Officer ²⁰ <div style="text-align: right;"> G.L.M. Krundenberg </div> | | |
| Date of the Actual Completion of the International Search ¹ 7th March 1984 | Date of Mailing of this International Search Report ³ 18 AVR. 1984 | | | | | | | |
| International Searching Authority ¹ EUROPEAN PATENT OFFICE | Signature of Authorized Officer ²⁰ <div style="text-align: right;"> G.L.M. Krundenberg </div> | | | | | | | |